SYNDROMES *

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> "He most honors my style who learns under it to destroy the teacher."—WALT WHITMAN, *Leaves of Grass*

IN the index of most textbooks of medicine or of special subjects, the word "syndrome"[1] is hardly ever mentioned. Certainly there is no section in any easily obtainable textbook where the *meaning* of the idea behind the word is even suggested.

We are supposed to know about syndromes, just as we are supposed to know what we mean by "consciousness" and "memory", "mechanism" and "function", "disease" and "symptoms". We have the convention that we may all use such terms with any shade of meaning which we like to give them from moment to moment. No definitions are required, nor are we supposed to have any historical sense of how they came into use. So we have a form of semantic ataxia, in which we stagger from one vagueness to another. The stepping-stones across the stream of ignorance often turn out to be foam-heaps of an outmoded form of scientific detergent.

Though the word "syndrome" has been used in English at least since 1541, and is defined by the *N.E.D.* as "a concurrence of several symptoms in a disease" or "a set of such concurrent symptoms", it is nowadays applied also to collections of signs, to mixed collections of symptoms *and* signs, and sometimes to a disease entity. It may apply even to special clinical test findings, as in Froin's syndrome [2]; or to a specific laboratory finding, as in the Guillain-Barré syndrome.[3] Occasionally we find the same name is attached both to a syndrome and to a disease. Thus we find Pick's disease (a form of presenile brain atrophy) and also Pick's syndrome.[4]

Some people think that the term syndrome should be used only for strange, apparently unconnected, collections of findings, as in Gerstmann's syndrome.[5]

We see, therefore, that the term is used somewhat loosely throughout medicine to signify certain collections of events, both in the patient and in the mind of his doctor.

Value and Uses of the Syndrome

The syndrome enables us to celebrate the great observers who made those conceptual advances which, though we take them for granted and have forgotten their origins, still direct our ways of thought. Against this may be set the fact that many, sometimes lesser, men have had their names attached to a supposed single clinical entity—often implying a specificity which is confusing and unjustified, apart from obliging us to remember the names both of the disease and of the man. The muscle-wasting diseases and disorders of the blood provide examples of this activity. Nowadays some effort is being made to link diseases with the name of the patient rather than that of the physician—as, for example, Christmas disease.

It is curious how whimsically the medical profession chooses one name rather than another to perpetuate a syndrome. Thus familial progressive hypertrophic interstitial polyneuritis is associated with the names of Déjèrine and Sottas who described it in 1893, and not with those of Gombault and Mallet who described it in 1889.

The syndrome provides a framework for learning clinical skill. Whenever one sets out to master a new subject one needs a set of principles upon which to work—a framework upon which to build with various materials. There are different sorts of buildings to be made—different constructs, such as we find in the different departments of the medical sciences. There are also various sorts of building materials—provided not only by the wide range of clinical material, and the special tests which can be applied to them, but also by the contributions of each teacher.

Undergraduates often make the mistake of thinking that teachers exist in their own right; and that their authority should be accepted without question, not only in their lectures and classrooms but also in their daily behaviour and way of life. This attitude is immature. Teachers are fairly well-paid providers of essentials for their pupils and for the community. A bad teacher, an indifferent teacher, is no better than a poor-quality grocer or an unreliable motor engineer. We do not use their services unless we have to. Even the best teachers have only certain things to teach. There must be gaps in their knowledge and wisdom.

Teachers are usually conscious of these defects. Perhaps the best teachers of all are those who teach how to learn rather than those who can provide every detail of a specialised subject. The student must recognise what academic syndrome each of his teachers shows, decide what he can learn from what the teacher says and does, and then pass on to another—much in the same way that he will change from medical clerking to surgical dressing, and then to special subjects such as obstetrics, nose-and-throat work, or clinical pathology, in the hope that finally he may have a balanced experience and knowledge from which to develop his own special skills and excellences. We need teachers who are logical in their handling of cases, who are firm in their decisions, who are kind to their patients, who are not afraid of psychiatry, and who like teaching. The student who discovers such teachers has already developed a certain syndromic system.

The syndrome illustrates the system of medical logic. When the earliest European university was set up at Salerno in 1224, the first law about medical education and practice carried the following stipulation:

> "Since students cannot be expected to learn medical science unless they have previously been grounded in logic, we further decree that no-one be permitted to take up the study of medical science without beforehand having devoted three full years to the study of logic."

* An address delivered in the introductory course of the Welsh National School of Medicine on May 13, 1959, at the suggestion of Prof. Harold Scarborough.

1. The *New English Dictionary* tells us to pronounce it *syn-dro-me*, as do our American colleagues. But British practitioners say *syn-drome*, and in England one may not correctly pronounce the word for fear of being considered affected.
2. A block in the cerebrospinal-fluid circulation, with high protein content shown by yellow colour and clotting of the fluid.
3. Acute infective polyneuritis, with high cerebrospinal-fluid protein but absence of cells.
4. Constrictive pericarditis, with pseudo cirrhosis of the liver.
5. Inability to identify fingers, acalculia, agraphia, and left-right disorientation.

Formal studies in logic no longer have any place in the medical curriculum, possibly because we have, in our books and our word-of-mouth clinical traditions, a vast subconscious system of logic, which sustains the whole framework of scientific knowledge and provides for every thought and act of clinical practice a precedent of proved validity. In everyday practice (and in all forms of research) our method is to apply a system of logical thought to the protean states of disease. The answer to any question about the significance of symptoms and signs, or about diagnosis, treatment or prognosis is:

1. We take a full history of the patient's life. Nothing is so small that it may be regarded as irrelevant (though practically we are usually forced to make the case take a certain shape).

2. We apply a number of tests to the patient's body. These tests give us a set of yes/no situations; for example: "Is the blood-pressure raised?"; "Is the patient dead?"; or even "Do I know what I am doing?". Having reached certain conclusions about the biography and biology of the patient,

3. We make use of ancillary tests (pathological, radiological, &c.), which may prove or disprove our contentions. We have then the sufficient number of yes/no combinations of a certain pattern so that we can match the combined pattern against a diagnostic pattern to get another yes/no situation: "Is it a tumour?"—"No." "Is it coronary thrombosis?"—"Yes." We have by now established the features of the syndrome, out of which should emerge appropriate treatment, and perhaps alleviation. And finally we can predict the future course of the disease—this is prognosis.

Evolution of the Syndrome

It has been wisely said that medical history is the story of a gigantic conflict between dogmatic tradition and experimental observation. We must consider the difficulties which opposed the pioneers who first tried to establish a scientific medicine. We have to imagine ourselves, three or four hundred years ago, tricked out in our university robes, from Padua like William Harvey, or like John Dee, who was in danger of losing his life for telling Queen Elizabeth that she was about to get smallpox (as she did a few days later), and who also "conjured at a poole in Brecknockshire, so that a wedge of gold was found".

We are going to a patient whose horoscope has been cast with an amazing degree of accuracy, quite comparable with the figures provided by the clinical pathology laboratories of today. A piebald horse crosses our path, two birds are circling overhead, and, on arrival at the patient's house, a black cat dashes out of the door. Indoors we find the patient unconscious, with his right arm and leg jerking. On recovery some hours later, he can no longer speak, and is weak down the right side. This is the one-horse, two-bird, black-cat syndrome of demonic possession, the cat being the vehicle in which the demon, having done his work, thought it prudent to leave.

There is nothing wrong with this reasoning; and we do not disagree with the Establishment. Nowadays we say that the horse and birds and cat had nothing to do with the case (unless the patient had been kicked by the horse, or scratched by the cat; or the birds were parrots): and we consider the case to be one of focal or jacksonian epilepsy, due to left-sided brain damage, leaving the patient with dysphasia and hemiplegia—probably a blood-vessel disorder, but possibly a tumour. But if one had said such things four hundred years ago, especially about the left side of the brain in right-sided paralysis, one might soon have been in a dungeon, next on the list for torture of a most compelling kind, to be mercifully completed by execution, probably by burning. It is not for nothing that the Jewish religion provides in the Day of Atonement ritual (*Yom Kippur*), a special dispensation of forgiveness for all oaths exacted under torture.

In those old days, only very few of the physicians would even realise that there was something the matter with their profession—just as we mostly live out our life content to apply what we have been told, doing what good we can, making enough money to ensure our way of living. The Renaissance physician would have to learn all the Hippocratic and Galenic traditions, and as much alchemy and astrology as he thought prudent. If he saw a new way of looking at things, it would come only as he was older, and after that almost impossibly difficult task of re-viewing everyday happenings. The ague had always been due to the damp air. Why should anyone take any notice of mosquitoes? Everyone got bitten by mosquitoes, but few got ague. What was the significance of that priest attending your classes—and then going off afterwards towards the cathedral? Were you suggesting a heresy—not only dangerous, but a sin as well?

Surely the early scientific physician was a great man, a new thinker of courage and determination, who followed the truth always in anxiety and peril. He found many patients, each with many symptoms and signs. The astrological and demonic history would be as complex as the modern assessment of psychological stress. He knew that there were many forms of disease. He had to give shape, as we do, to the problems he had chosen to tackle. He must have noticed, for example, that most patients, and he himself, had headaches from time to time: and that a very small number of patients who complained of headaches eventually died after having had (as we would say now) mental changes, fits, loss of vision, paralysis, drowsiness, and coma. Only after many years, and after hearing the experience of his colleagues, could he say "all the patients who had headaches of a certain pattern, who had failure of vision, and who had convulsions and so on, eventually died in a certain way—coma". Unless he was able to dissect the dead body of the patient and compare his findings with those found in patients for other reasons, he could never say "in most of those cases which had headache, &c., there was found in the head, of all places, a lump (on the opposite side from the paralysis) which was not to be found in the head of almost every person who died by having his head cut off". Dissection was dangerous, because of infection, the law, and public opinion. For any one physician material must have been scarce, because no-one was alert to the possibility of brain tumour. The findings in normal subjects were little known, and even Leonardo's drawings are surprisingly inaccurate.

But the task was eventually accomplished. And we have today the whole process before us: of the physician moving from passive experience to positive observation, then to the collection of records, and the writing of papers and books; then to pathological studies. And so to controlled reasoning. Such a process results, after hundreds of years, in the capability of a second-year clinical student of modern medicine to make a diagnosis with an accuracy that would have exceeded beyond any imagination the powers of the ablest physicians of two hundred or even one hundred years ago. How important it is that we do not forget that the process must continue!

We owe these powers to the skill and rational thought of our forebears. Too little do we remember to acknowledge our debt not only to the physicians and surgeons of the

past, but also, as Wilfred Trotter pointed out, to the patients who deliberately provided the opportunity for advance.

Medical Symbolic Logic

We may now begin to see that the syndrome represents an unconscious medical logical system. It is the algebraic formula in medicine. Symptoms are symbols of disordered functions. The development of these symptoms provides other symbols. Symptoms and their evolution are associated with physical signs, which also are symbols. Special tests provide additional symbols. By addition, multiplication, time-scaling, and so on, we find that the patient has, say, bacterial endocarditis. He satisfies a formula of the gradual development of illness with fever, anæmia, clubbing, splenomegaly, on the basis of some form of heart disorder, plus a positive blood-culture and a good response to antibiotic treatment. If the patient has all the ingredients of the formula, there will be no doubt about the diagnosis. Patients hardly ever do have all the ingredients at the stage where the diagnosis is worth making from the prognostic point of view. They have some of the terms, but may lack one or more of the cardinal ones. The physician then has to make his diagnostic graph of the equation by choosing the points which best suit his notion of the case. He draws the likely graph of the condition. Of course, the fewer correct points there are, the more speculative the graph becomes (as it does in physics and chemistry and geometry). The graph may eventually diverge so much from what it should be that another outline may appear, resembling the graph of a different disease, such as typhoid fever or chronic meningococcal septicæmia.

This system of medicine which we all use, and which the student has to learn, is of great practical value and is as " scientific " as any other method of science. It is far more difficult than the planned isolated experiment, for it has to take what any patient happens to present. It has to deal with such a vast subject that the numbers of possible combinations make neat statistical results almost impossible to achieve. Thus today results show that arteriosclerosis and coronary-artery disease are due to saturated animal fats in the diet: that they are not due to these fats: that disseminated sclerosis is due to a virus; that it is due to allergy: that skin conditions are quite separate from emotional stress; or, as I personally believe, that they are closely related to emotional stress.

For medical practice we have to learn some outline of clinical assessment and then see exactly how our patients fit our formulæ, or syndromic patterns. By this method, a syndrome may be subdivided, so that, for example, epilepsy is not always convulsions due to demonic possession and the unspecified wickedness of a great-grandfather, but also may be due to a temporary preponderance of the influence of evil spirits over guardian angels; or to the personal wickedness of having a motor-cycle from which one has fallen; or to a lump inside the head that may, by the production of fits, be doing one the good turn of asking one to get a surgeon to remove it.

We therefore see that the syndrome represents the culmination of medical endeavour; for a syndrome comprises all those features by which we describe a disease, and embodies the distilled or abstracted knowledge of the total experience of the medical and other, allied, scientific professions. For final example, in the three medical algebraic words " Brown-Séquard syndrome " we bring to mind that amiable unstable genius of an English physician from Mauritius, who died a Frenchman in Paris; who was a fellow of the Royal Society, and of the Royal College of Physicians of London; who practised in London, Paris and New York; who was appointed a founder physician of the National Hospital, Queen Square, a hundred years ago; who made sixty crossings of the Atlantic; who was a pioneer in animal experiment, in endocrinology, and in the study of the autonomic nervous system; and who described the patient with weakness and one form of sensory loss on one side of the body and a different form of sensory loss on the other side—the patient who may have a broken neck or a gun-shot wound or a spinal tumour, who needs to be in hospital for several special tests, who may not have long to live, or who may be cured by certain measures you will devise.

Conclusion

Syndromes are the signpost and compass and map, which direct us through the crowded twisting streets, the oceans, and the jungles of medical experience. They are not points of arrival, nor things. They are not immutable, and are always to be reviewed critically. A full understanding of the logical system implied by the syndrome should enable us to guide our patients with confidence and wisdom; should suggest and direct our researches; and should refresh our sense of gratitude to our medical forefathers.

I wish to express my gratitude to Sir Francis Walshe, F.R.S., and to Dr. Walther Riese of Richmond, Virginia, who have both, in their separate ways, shaped much of my thought. They have not been consulted about this paper, and are not responsible for any of the defects which it may contain.

THE INFLUENCE OF DIET ON SERUM-TRIGLYCERIDES

In South African White and Bantu Prisoners*

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AN investigation was recently conducted on fasting serum-triglyceride levels and fatty-acid composition in the two main racial groups living in South Africa—namely, (1) the whites, whose diet in the main is similar to that of most people of the Western hemisphere (i.e., containing about 40% of calories derived mainly from animal fat), and (2) the Bantu, whose diet in general contains less than 15% of calories from fat, and is high in carbohydrate content (Antonis and Bersohn 1960).

This study showed that ischæmic-heart-disease patients of both sexes, and white males over 40, had fasting serum-triglyceride levels significantly higher than those of young white males or premenopausal females, and of Bantu males of all ages; and, furthermore, high triglyceride levels were associated with a greater degree of saturation of the fatty-acid components. In view of the widely differing incidence of ischæmic heart-disease among these subjects—rare in the Bantu but becoming increasingly prevalent among younger white males—it was suggested that raised serum-triglyceride levels may be the

* This study forms part of the programme of a prison research project on diet and metabolism relating to cardiovascular disease conducted by the South African Council for Scientific and Industrial Research, and it is published with their permission.

result of faulty fat transport and clearance mechanisms (either produced or aggravated by excessive intake of dietary fats rich in saturated fatty acids), and that ischæmic heart-disease may result from a faulty triglyceride metabolism brought about by the habitual consumption of such diets.

Since 1957 we have participated in a research project on diet and metabolism relating to cardiovascular disease at the Pretoria Central Prison in collaboration with the South African Council for Scientific and Industrial Research, the South African Institute for Medical Research, the National Nutrition Research Institute, and other interested bodies, under the leadership of Prof. P. J. Kloppers. During this investigation we studied the influence of short-term and long-term dietary manipulation on fasting serum-triglyceride levels.

Subjects and Dietary Changes

A detailed report on the clinical status and selection of the volunteers will be published elsewhere. None of them showed any clinical manifestations of ischæmic heart-disease or other disease.

Electrocardiography and exercise-tolerance tests were performed regularly under the supervision of a physician specialist. All volunteers underwent full biochemical screening, which included complete lipid studies liver-function tests, and serum-protein electrophoresis, as well as having full blood-counts and erythrocyte-sedimentation rates at regular intervals. Only volunteers whose screening tests were within the accepted range of normality were included in this investigation, but we would emphasise that a wider range for liver-function tests had to be accepted for the Bantu volunteers, since by white standards only very small numbers of the South African Bantu population would be considered normal. No volunteers were accepted whose liver-function tests were grossly abnormal, and in all cases the bromsulphalein dye-retention tests at the end of 45 minutes (5 mg. per kg. body-weight) were within normal limits.

All volunteers were long-term prisoners whose ages ranged from 21 to 54 years (whites 29–54 years, mean 38 ± 7 years; Bantu 21–50 years, mean 37 ± 9 years). White volunteers performed a normal day's work involving carpentry and typographical and/or other artisan labour. Bantu volunteers did less skilled labour, such as cleaning and sweeping. In no case was hard labour, such as stone breaking, performed by any of the volunteers. Before the project was initiated volunteers had subsisted for 1 month to 15 years on a normal prison diet, which is very similar in composition to the basal diet used in this study (whites 4 months to 15 years, mean 31 ± 33 months; Bantu 1 to 56 months; mean 14 ± 13 months).

The total food intake contained about 3000 calories per day, and diets were kept at this level throughout the experimental period. The protein content of the diet was about 15% of the total daily caloric intake.

Dietary Regimes

Diets were manipulated in order to assess the influence of:

Change from low-fat/high-carbohydrate to high-fat/low carbohydrate calories.

Different kinds of fat at the 40% caloric level.

Change from high-fat/low carbohydrate to low-fat/high carbohydrate calories.

Diet 1.—This diet contained about 15% of fat calories from the fats and oils of the meat and vegetable foods, and 70% carbohydrate calories.

Diet 2.—The fat-calorie content of diet 1 was increased to 40% by isocaloric substitution of different oils and fats for carbohydrate, which was reduced to 45% of the total calories. The volunteers were divided into three groups: (I) had sunflower-seed oil (containing 63% linoleic acid) as the fat substitute, (II) had partially hydrogenated sunflower-seed oil (containing no linoleic acid); and (III) had additional fat calories derived from butter.

Interim diets 2a, b, and c.—The fat composition of diet 2 was manipulated at the 40% caloric level, to contain at first a 50 : 50 mixture of sunflower-seed oil and butter (diet 2*a*), and later a 75 : 25 mixture of sunflower-seed oil and butter (diet 2*b*). These two diets were consumed immediately after diet 2 and just before diet 2*c*, when volunteers were redivided into two groups. Those who originally had the butter substitute in diet 2 now received oil, while those who had had the oil were given a butter substitute. The volunteers who had initially received the partially hydrogenated oil were given either oil or butter substitutions.

During these dietary changes a number of volunteers resigned from the project and additional volunteers were included as replacements. Thirty of the original volunteers (fifteen white and fifteen Bantu), however, continued for the full trial. After the start of diet 2, five white and seven Bantu additional volunteers were included, who subsisted on the high-fat-calorie diets for a shorter period (i.e., 74 weeks) than the original volunteers before the fat-calorie content was reduced for diet 3. A further twelve volunteers (eight white and four Bantu) were also included at the start of diet 2*c*, and subsisted for only 8 weeks on the high-fat-calorie diet before diet 3.

Diet 3.—The fat content was reduced to the original 15% calories of diet 1.

Duration of Diets

Diet 1, 39 weeks; diet 2, 51 weeks; interim diets 2*a*, *b*, and *c* for 18, 19, and 8 weeks respectively; and diet 3, 32 weeks.

Experimental Procedure

All specimens of blood were drawn early in the morning before breakfast and after an overnight fast of 12 hours.

Triglycerides were estimated on phospholipid-free serum extracts directly according to the fluorimetric procedure of Mendelsohn and Antonis (1960), and indirectly by the ester-group method of Antonis (1960), which required parallel estimation of cholesteryl ester concentration by the method of Sperry and Webb (1950). Analyses were also made on serum-total-lipid extracts by other methods described previously (Antonis and Bersohn 1960). The latter extracts were fractionated by the silicic-acid chromatographic technique of Barron and Hanahan (1958), and triglyceride polyenoic fatty acids were estimated after alkali isomerisation by the ultra-violet spectrophotometric method of Holman and Hayes (1958). Towards the end of the study the fatty-acid composition of the triglycerides was estimated by gas-liquid chromatography on a Pye argon-gas chromatograph, utilising an argon-ionisation detector with a radium foil. A 120 mm. glass column (4 mm. internal diameter) filled with 80–100 mesh chromosorb on which 20% polyethyleneglycol adipate was coated, was used for analysis at 195°C with a gas flow-rate of 80 ml. per minute. Peak areas were measured by triangulation and analyses were performed at two or more levels.

Triglycerides (containing also diglycerides and monoglycerides, unesterified fatty acids, and free cholesterol from the silicic-acid fractionation) were methylated by interesterification under reflux for 2 hours with 3·5% methanolic sulphuric acid. After partial evaporation of the reaction mixture and neutralisation with 8% aqueous sodium-bicarbonate solution, the fatty-acid methyl esters were extracted with petroleum ether (boiling point 30–60°C), and stored in the cold until analysed. The free cholesterol obtained with the esters was not removed since it does not interfere with the gas chromatographic separation (Dr. S. R. Lipsky and Dr. J. E. Lovelock, personal communication). The sterol, however, crystallised in the cold from solution in the methyl esters. Thus before analysis, aliquots of the petroleum-ether extracts were evaporated to dryness under nitrogen, and sufficient xylene was added to maintain the residue in a liquid state at room temperature. This high boiling solvent, which was not retained on the polar column at the temperature used, was eliminated immediately after the air peak, and did not interfere with the subsequent elution pattern.

Results

CONCENTRATION OF FASTING SERUM-TRIGLYCERIDES

The individual fasting serum triglyceride levels of volunteers of both races on the first two diets are shown

TABLE I—INFLUENCE OF DIETARY FAT ON SERUM-TRIGLYCERIDE LEVELS
(mg. per 100 ml. serum) E=whites; B=Bantu

Volunteer	Diet 1	Diet 2 (oil)		Volunteer	Diet 1	Diet 2 (fat)		Volunteer	Diet 1	Diet 2 (butter)	
		22 weeks	51 weeks			22 weeks	51 weeks			22 weeks	51 weeks
E2 ..	107	87	81	E10 ..	92	101	112	E1 ..	65	118	128
E5 ..	116	110	95	E18 ..	60	107	167	E3 ..	98	86	108
E6 ..	100	113	118	E20 ..	116	141*	..	E4 ..	64	114	99
E8 ..	87	66	61	E22 ..	86	99*	..	E7 ..	110	99	97
E11 ..	80	101	114	E24 ..	61	152	140	E12 ..	90	86	88
E13 ..	73	70	66	E25 ..	97	93	111	E21 ..	87	97	149
E16 ..	68	55	50	E28 ..	99	155	138	E23 ..	79	101	142
E17 ..	74	81	73					E26 ..	74	122	151
E19 ..	107	91	79					E29 ..	108	108	113
Mean	90·2	86·0	81·9		87·1	121·1	133·6		86·1	103·4	119·4
S.D.	16·6	18·9	21·9		19·0	25·0	20·8		16·1	12·3	22·4
B11 ..	57	53	53	B1 ..	89	85	90	B7 ..	77	88	147
B14 ..	80	83	86	B9 ..	60	89	101	B10 ..	83	142	100
B16 ..	147	133	106	B12 ..	86	129	..	B13 ..	87	105	124
B18 ..	111	77	81	B17 ..	65	118	143	B20 ..	82	118	147
B19 ..	62	93	93	B22 ..	68	128	128	B21 ..	90	93	186
B23 ..	127	100	101	B27 ..	83	84	111				
B24 ..	118	97	55	B28 ..	87	111	..				
B30 ..	89	69	81								
Mean	98·9	88·1	82·0		76·9	106·3	114·6		83·8	109·2	140·8
S.D.	30·0	22·4	18·2		11·2	18·5	18·9		4·4	19·4	28·5
For whole group: Mean	*94·3*	*87·0*	*81·9*		*82·1*	*113·7*	*124·1*		*85·3*	*105·5*	*127·1*
S.D.	*24·2*	*20·6*	*22·5*		*16·4*	*23·2*	*22·0*		*13·2*	*15·5*	*26·8*

Diet 1 (base diet).—15% fat and 70% carbohydrate calories. Total intake 3000 calories per day.
For all volunteers: mean = 87·7 ± 19·7 mg. per 100 ml. serum.
Whites 87·9 ± 17·3, and Bantu 87·4 ± 22·4 mg. per 100 ml. serum, respectively.
Diet 2.—40% fat and 45% carbohydrate calories (15% fat calories as in diet 1, extra 25% derived from oil, hydrogenated oil [fat], or butter).
* 16 weeks after change of diet.

in table I. Although forty-eight volunteers completed the course of the first diet, only forty-five continued for the second diet, and the results for these latter subjects only are included in the table.

Diet 1 (Basal)

For the first diet the values shown represent the individual means of two estimations taken after a 2-month interval. The mean individual variation for the white volunteers † was 6·5 mg. per 100 ml. serum, while for the Bantu volunteers this was 7·2 mg. per 100 ml. serum. The mean triglyceride levels of the two volunteer groups on the first three diets were not significantly different from each other on a racial basis, and the groups have therefore been considered as a whole, with a mean individual variation of 6·8 mg. per 100 ml. serum. For the forty-five volunteers whose individual levels are shown in the table, the mean fasting serum-triglyceride level on the first diet was 87·7 ± 19·7 mg. per 100 ml. serum (whites 87·9 ± 17·3, and Bantu 87·4 ± 22·4 mg. per 100 ml. serum respectively). The remaining three volunteers—E27, E30, and B5—had levels of 37, 100, and 46 mg. per 100 ml. serum respectively.

Effect of Increasing and Changing the Fat Calories

Diet 2.—The values in table I represent estimations made 22 and 51 weeks after the change from diet 1. The changes from the basal diet to the high-fat diet after 51 weeks are also shown graphically in fig. 1.

Oil groups.—Although there was a tendency for values to fall (except for two white and two Bantu volunteers) no differences were significant.

Partially-hydrogenated-oil (fat) groups.—Volunteers of both racial groups responded to the dietary change in the same way. Each racial group showed a gradual increase in the mean serum-triglyceride level as compared to that on the first diet. 22 weeks after the change the probability that the differences were significant was $0{\cdot}02 < P < 0{\cdot}05$ in each case, and for the two groups combined $P < 0{\cdot}01$. 51 weeks after diet 1, however, all differences were highly significant ($P \leqslant 0{\cdot}001$).

† Calculated as the standard error of a single determination, S.D. $= \sqrt{\frac{\Delta^2}{2n}}$, where Δ is the difference between two single tests performed on each sample, and n is the number of double determinations.

One Bantu volunteer, B1, showed no change on either of the above diets.

Butter groups.—The results were almost identical with those shown by the fat groups—i.e., after 22 weeks $0{\cdot}02 < P < 0{\cdot}05$ for each group, and for the two groups combined $P < 0{\cdot}01$. After 51 weeks, all differences were highly significant ($P \leqslant 0{\cdot}001$).

Two white volunteers, E7 and E12, showed no change on any diet.

Interim diets 2a, b, and c.—Diets 2*a* and *b*, involving mixtures of sunflower-seed oil and butter, were consumed

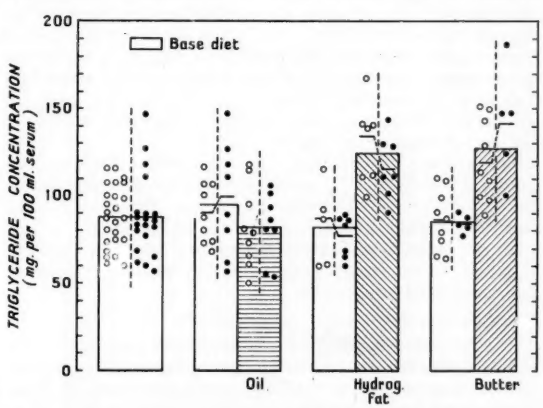

Fig. 1—Influence on fasting serum-triglyceride levels of increasing the proportion and altering the nature of the dietary fat calories.

Results are shown for the base diet (15% fat, 70% carbohydrate calories) as unshaded bars, and after a year on the high-fat diets (40% fat, 45% carbohydrate calories) as shaded bars. The first unshaded bar represents the mean for all volunteers on the base diet. The subsequent unshaded and shaded bars represent the means for each group of volunteers before and after the dietary change respectively. Open circles represent white volunteers; closed circles, Bantu volunteers. The tops of the bars represent the mean values for both groups of volunteers combined. The short bars above and below the means for the combined groups represent the means for each racial group; where no short bars are shown the means for the racial and combined group are identical. Serum-triglyceride levels on the hydrogenated-oil and butter diets are significantly higher than they are on the base diet ($P \leqslant 0{\cdot}001$).

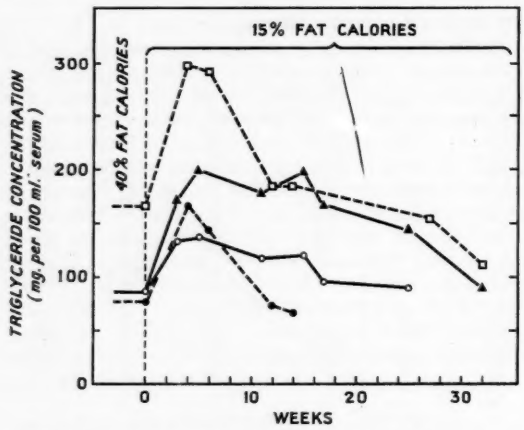

Fig. 2—Influence on fasting serum-triglyceride levels of reducing the proportion of fat calories.

The upper continuous line represents the means of 32%, and the lower continuous line the means of 68%, of the white volunteers. The upper interrupted line represents the means of 12%, and the lower interrupted line the means of 88%, of the Bantu volunteers.

successively by all volunteers for a total period of 27 weeks immediately after diet 2. No results are shown for these changes, because fasting serum-triglyceride levels were only estimated irregularly on a few cases. The tendency, however, was for values reached on the butter and hydrogenated-oil diets to fall, and before diet 2*c*, most of the volunteers had fasting triglyceride levels similar to their basal values on diet 1. Volunteers consumed diet 2*c* for a relatively short period (8 weeks) directly after the interim diet 2*b*.

The white volunteers who were maintained on the oil diet (2), showed a considerable rise in their serum-triglyceride levels when consuming the butter diet (2*c*). Differences were not assessed for significance, however, since the volunteers had subsisted for a long time on the mixed oil/butter diets before changing to the butter diet. The values for the corresponding Bantu volunteers, on the other hand, remained low on the butter diet 2*c* except for volunteers B16 and B23, both of whom had high fasting serum-triglyceride levels on the base diet. A replacement Bantu volunteer, who had a high level on the oil diet, also showed an increase on the butter diet.

Two volunteers—E18 and E25—who were initially on the hydrogenated-oil diet (2) responded differently to the butter diet (2*c*), the former showing an increase whereas the latter showed no change compared to the base levels.

All volunteers of both races who consumed diet 2*c*, containing oil, had low serum-triglyceride levels, not significantly different from their basal level on diet 1.

Effect of Decreasing the Fat Calories

Fasting serum-triglyceride concentrations responded very rapidly when the diets were changed from a 40% fat/45% carbohydrate to a 15% fat/70% carbohydrate calorie level. These changes are illustrated in fig. 2.‡

White volunteers.—All volunteers (irrespective of the nature of the dietary fat in diet 2*c*) showed immediate significant rises in their fasting serum-triglyceride levels when the fat calories were replaced by carbohydrate, the peak values being reached by about the 5th week after the change. These high levels subsided slowly and by the 17th week the mean level for the whole group was still higher than either the base level on diet 1, or the level on diet 2*c* just before the change. Although the fasting serum-triglyceride levels of about 68% of the volunteers had returned to their base values, the remainder still had relatively high levels which only returned to the base after 32 weeks.

‡ Multigraphed copies of the detailed results from which fig. 2 and table III were derived may be had from *The Lancet*, 7, Adam Street, London, W.C.2.

Bantu volunteers.—The immediate response to the change in the proportion of fat calories was even greater for the Bantu than for the white volunteers. Higher peak levels were reached in the former, but these subsided very much more rapidly, and by the 12th to 14th week 88% of the volunteers had fasting levels under 100 mg. per 100 ml. serum. Two volunteers (B16 and B23), who had high fasting levels on either the base or the high-oil-calorie diets, showed a similar pattern to that of 32% of the white volunteers, and their base levels were only reached after 32 weeks.

On diet 2*c*, irrespective of the nature of the dietary fat, the fasting triglyceride levels of the final group of replacement volunteers were still low after 8 weeks. When their dietary fat-caloric content was reduced, both Bantu and white replacement volunteers showed the same initial increase in their fasting serum-triglyceride levels as the other volunteers, even though the former had had the high-fat diet for only a relatively short period.

SERUM-TRIGLYCERIDE FATTY-ACID COMPOSITION

The fatty-acid composition of the various diets was not analysed. But, since 15% of the fat calories (derived mainly from the meat of the diet) were unaltered throughout, the changes in the serum-triglyceride fatty-acid pattern can be compared in relation to the composition (shown in table II) of the dietary fat substituted for carbohydrate—i.e., 25% of the total fat calories.

The mean serum-triglyceride polyenoic fatty-acid patterns of all volunteers on the various diets are shown in table III.

TABLE II—FATTY-ACID COMPOSITION OF DIETARY FAT
(% of total fatty acids)

Major fatty acid	Sunflower-seed oil	Hydrogenated sunflower-seed oil	Butter
Lauric (C12 : 0) ..	..	..	1·4
Myristic (C14 : 0)	..	..	9·9
Palmitic (C16 : 0) ..	7·5	7·8	31·8
Palmitoleic (C16 : 1) ..	..	..	2·2
Stearic (C18 : 0) ..	4·1	17·4	13·5
Oleic (C18 : 1) ..	24·7	73·1	29·2
Linoleic (C18 : 2) ..	63·7	1·6	0·8

These values were obtained by the alkali-isomerisation procedure. The patterns were not significantly different on a racial basis, and since each group responded in an identical manner to the same diets, the results for both racial groups have been combined. Even after a relatively short period on a particular diet the composition of the serum-triglyceride polyenoic fatty acids appeared to have stabilised, and results obtained 22 and 51 weeks after a particular dietary change (diet 2) were only slightly different from those after 8 weeks (diet 2*c*).

When part of the carbohydrate of the basal diet was changed to butter or hydrogenated sunflower-seed oil, there were no significant changes in the serum-triglyceride polyenoic fatty-acid pattern. The similar change by substitution of sunflower-seed oil, however, caused a significant increase in the proportion of dienoic fatty acids. Unfortunately the gas-liquid chromatographic method was not available to us for analysis of total fatty

TABLE III—INFLUENCE OF DIETARY FAT ON SERUM-TRIGLYCERIDE POLYENOIC FATTY-ACID COMPOSITION

Dietary fat calories		Total fatty acids (%)				
		Dienoic	Trienoic	Tetraenoic	Pentaenoic	Hexaenoic
15%		18·3	4·0	3·6	1·3	3·7
40%	Butter	19·0	4·3	4·4	1·7	2·5
	Hydrogenated oil	18·3	4·0	3·8	1·1	1·6
	Oil	50·1	5·4	4·2	1·0	2·8

Values were obtained by means of the alkali isomerisation technique of analysis.

TABLE IV—INFLUENCE OF DIETARY FAT ON SERUM-TRIGLYCERIDE TOTAL-FATTY-ACID COMPOSITION
(% total fatty acids)

Major fatty acids *	15% fat calories (diet 3)		40% fat calories (diet 2c)			
			Butter		Oil	
	Whites	Bantu	Whites	Bantu	Whites	Bantu
C14 : 0 Myristic	1·6	1·5	2·3	3·5	0·9	0·8
C14 : Br	0·1	Trace	0·4	0·5	0·1	0·1
C15 : 0	0·2	0·1	0·7	0·6	0·3	0·2
C14 : 3	0·1	Trace	0·3	0·3	0·1	0·2
C16 : 0 Palmitic	24·2	28·8	26·9	32·4	16·3	16·1
C16 : 1 Palmitoleic	6·1	7·8	3·8	2·3	2·5	1·3
C16 : 2	1·0	1·3	1·5	0·6	1·4	0·4
C18 : 0 Stearic	5·4	3·9	5·3	6·7	3·8	4·2
C18 : 1 Oleic	42·9	37·2	34·7	30·1	20·9	22·9
C18 : 2 Linoleic	18·0	18·4	17·8	18·6	48·9	49·0
C18 : 2 (?)	Trace	Trace	0·6	Trace	0·5	0·1
C18 : 3 Linolenic	Trace	Trace	Trace	Trace	Trace	Trace
C20 : 2	—	—	Trace	Trace	0·3	0·2
C20 : 3	Trace	Trace	1·2	0·8	0·5	0·5
C20 : 4 Arachidonic	1·0	1·1	3·6	3·2	2·8	3·8
C22 : 5 and C22 : 6	Trace	Trace	Trace	Trace	Trace	Trace

* Shorthand designation, according to Ahrens et al. (1959).

Diet 3.—15% fat calories from meat and vegetables.
Oleic/stearic acid ratio = 8·75 (mean of white and Bantu ratios).

Diet 2c.—15% fat calories as in diet 4, 25% fat calories from sunflower-seed oil (oleic/stearic ratio = 5·5) and butter (oleic/stearic ratio = 5·4) (means of white and Bantu ratios).

Analyses were made on pooled serum-triglyceride extracts using the gas-liquid chromatographic technique.

acids during the initial part of the study, but analyses of the serum-triglyceride fatty acids on diets 2c and 3 were made by this technique. Table IV and fig. 3 show the analysis of pooled serum-triglyceride specimens on the butter, sunflower-seed oil, and basal diets. Not only were the polyenoic fatty-acid patterns obtained on diets 2c (butter) and 3 (base) almost identical but also examination of the total-fatty-acid patterns reveals that the proportion and nature of the other fatty-acid constituents were also very similar.

The major changes produced in the serum-triglyceride fatty-acid patterns of the basal diet by an increase in the nature and proportion of the fat calories were as follows:

By sunflower-seed oil.—The linoleic-acid content increased with a proportional decrease in that of palmitic, palmitoleic, and oleic acids. The stearic-acid content was unchanged, and the ratio of oleic to stearic acids was decreased from 8·75 to 5·5.

By butter.—The content of palmitic and stearic acid increased while that of palmitoleic and oleic acids fell, the ratio of oleic to stearic acids again decreasing to 5·4.

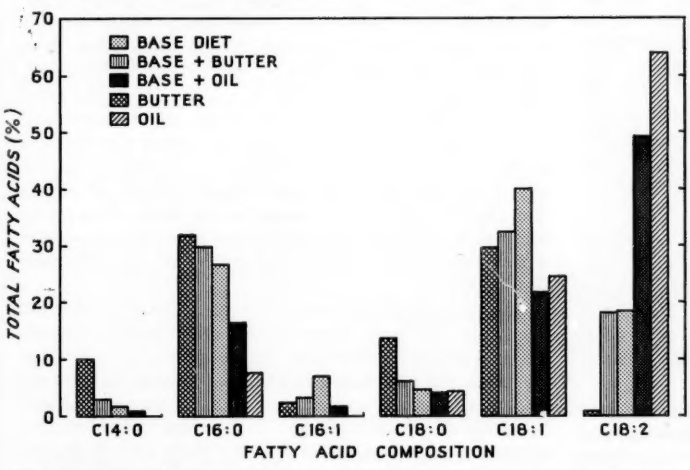

Fig. 3—Influence of dietary sunflower-seed oil and butter on serum-triglyceride fatty-acid composition.

The first and fifth bars for each fatty-acid component represent the composition of the dietary fat; the third bar represents the proportion of fatty acid in the basal serum-triglyceride; and the second and fourth bars represent the proportion of fatty acids in the serum-triglycerides on the high-fat diets.

The serum-triglyceride fatty-acid composition clearly reflects that of the dietary fat.

Discussion

Changes Produced by Increase and Alteration of Fat Calories

The results in the present study show that white and Bantu subjects, when subsisting for a long time on a particular diet (either high or low in fat-caloric content), have fasting serum-triglyceride levels not significantly different from each other; and, furthermore, the composition of their serum-triglyceride fatty-acid components is almost identical. Changes both in the nature of the calories (by substitution of fat for carbohydrate), or in the type of fat consumed at the 40% caloric level, produced an identical response in each racial group. Fæcal lipid excretion was also very similar in these two groups (to be published separately), and it is apparent that no significant racial differences exist in the mechanisms of fat transport, utilisation, and excretion when these groups are habituated to the same diet.

On the basal diet, containing 15% of fat calories, the mean fasting serum-triglyceride level of both groups combined was 87·7 ± 19·7 mg. per 100 ml. serum. Fasting serum-triglyceride levels of both groups showed a progressive response to increase in the fat-calorie content from 15 to 40%. The replacement volunteers included towards the end of the study consumed the high-fat diet for 8 weeks only, and their fasting serum-triglyceride levels at the end of this period were still low. Although basal values were not obtained for this group before the initiation of the high-fat diet, there were no significant changes when they were subsequently habituated to the low-fat diet. This would indicate that the immediate response to an increase in the proportion of fat calories was negligible, a finding also confirmed by other workers (Ahrens 1957). In the early part of this study values were estimated at relatively long periods after the change in the proportion of the dietary fat calories. 22 weeks after the change to hydrogenated oil or butter, the fasting serum-triglyceride levels were just significantly greater than the corresponding levels on the 15% fat-calorie diet; by 51 weeks, however, the increase was highly significant. The period of habituation to the saturated fat diet was only a year, but even in this relatively short time significant changes had occurred, and the mean serum-triglyceride levels of both racial groups combined (124·1 and 127·1 mg. per 100 ml. respectively) were higher than the upper limit of normal (114 mg. per 100 ml. serum) suggested in our previous study (Antonis and Bersohn 1960). In contrast to their response to the saturated fat diets, both groups of prisoners, when consuming the sunflower-seed-oil diet, maintained their low basal serum-triglyceride levels (whites 81·9 and Bantu 83·0 mg. per 100 ml. respectively).

Our previous study of these racial groups, when subsisting on their natural diets, indicated significant differences, particularly when older subjects were compared, both in the absolute fasting serum-triglyceride levels and in the composition of the fatty acids. These differences were slight when young subjects of both races were compared, but they became more significant with increasing age because the Bantu subjects showed no age trend while the levels of the white subjects increased with increasing age.

The present study indicates that the consumption of diets low in fat calories or high in vegetable oils (i.e., rich in the proportion of highly unsaturated fatty acids) keeps serum-triglyceride levels low, whereas high-fat-calorie diets, which are rich in their content of saturated fatty acids raise the serum-triglyceride levels. The nature of the fat calories in high-fat-calorie diets is therefore of considerable importance in controlling the absolute serum-triglyceride level, and the age trend among the white subjects consequently appears to be a result of habituation to the high-saturated-fat diet; their triglyceride metabolic processes alter in some way and lead to increased serum-triglyceride levels with increasing age—the process apparently being more rapid in some people than others. Habituation to low-fat diets, on the other hand, has no such effect, and the low serum-triglyceride levels of the Bantu subjects (75 mg. per 100 ml. serum) appear to be primarily related to their low-fat-calorie diet—an observation confirmed in the present study by the low serum-triglyceride levels of the white prisoners when habituated to the Bantu-type low-fat-calorie diet (87·9 mg. per 100 ml. serum).

While the basal diet in the present study and the natural urban Bantu diet have a similar fat-calorie content (15%), the nature of the fat constituents in these diets differs considerably. The former diet, which contains considerably more meat and less whole maize than the latter (Higginson and Oettlé 1960), is much poorer in its content of linoleic acid. This may account for the lower proportion of linoleic acid in the serum-triglycerides of the volunteers on the basal diet as compared to that of the urban Bantu in the previous study (18·3% as against 30·7%), and it seems to be confirmed by the changes in the triglyceride fatty-acid patterns produced by the different high-fat-calorie diets.

Comparison of the results in tables II and IV (shown graphically in fig. 3) indicates that the fasting serum triglyceride total-fatty-acid composition strongly resembles that of the dietary fat substituent, as was previously reported by Ahrens et al. (1959). In this study, when menhaden oil was used as the sole dietary fat, the linoleic-acid content of the serum-triglyceride fatty acids fell to 8·4% in one patient. Since the corresponding proportion of serum-triglyceride linoleic acid in our study showed virtually no change from 18% with the basal or the high-butter-fat diets, it seems either that the former diet still contained a fair proportion of linoleic acid (probably of vegetable origin), or that the subjects were capable of synthesising linoleic acid from endogenous sources.

Although the low serum-triglyceride concentrations produced by the high-fat-calorie sunflower-seed-oil diet are clearly associated with a significant increase in the proportion of linoleic acid in the fasting serum-triglycerides, whereas on saturated fat diets the proportion of linoleic acid in the raised serum-triglyceride levels is considerably lower, the reasons are not clear.

Mead and Fillerup (1957) have shown that dietary fatty acids are incorporated at different rates into the various blood-lipid components:

> They found that when carboxy-labelled stearate, oleate, and linoleate were fed to rats, a distinctively large amount of the labelled linoleate appeared very rapidly in the plasma phospholipids, whereas with oleate and stearate incorporation into the phospholipids was very much slower. Since all these fatty acids enter the blood almost entirely as triglycerides in lymph chylomicrons, they suggested that this indicated rapid preferential incorporation of linoleate into higher-density lipoproteins of the blood.

In our study, therefore, triglycerides of different fatty-acid composition may also have different plasma turnover rates (e.g., trilinolein may be transported away from the plasma at a faster rate than triolein or tristearin), which may then influence other triglyceride metabolic processes of fat clearance and utilisation. Habituation to diets rich in unsaturated fatty acids may therefore lead to increased rates of triglyceride removal from the blood-stream, resulting in lower residual serum-triglyceride levels. Conversely, habituation to high-saturated fat diets may decrease fat-clearance rates, the net result being elevated residual serum-triglyceride levels.

Our studies with ^{131}I-triolein in white and Bantu subjects on their natural diets (Metz et al. 1960) lend strong support to this view. We found that the ingestion of ^{131}I-triolein leads to lower initial levels of plasma radioactivity in Bantu than in white subjects with and without ischæmic heart-disease. Furthermore in the Bantu the peak values tended to arise earlier after the ingestion of the fat load. The measured levels of radioactivity represent a resultant of absorption into, and clearance from, the plasma and, since absorption rates were similar in all the subjects, it was inferred that the rates of removal of fat from the plasma were different, and that this may have accounted for the raised fasting serum-triglyceride levels in the older white subjects and ischæmic-heart-disease patients. Although similar investigations have not yet been made on the volunteers in our present study, it could be inferred by analogy that the raised serum-triglyceride levels produced by the high-saturated-fat diets may also be due to altered fat-clearance rates.

Changes Produced by Decreasing the Fat Calories

When the proportion of dietary-fat calories was reduced from 40% to 15%, certain racial and inter-racial differences soon became apparent. While the fasting serum-triglyceride levels of 88% of the Bantu volunteers had returned to their low base levels within 12–14 weeks, the corresponding values for the white volunteers were still raised, base levels being reached by 68% only after 17–20 weeks. At this stage the remaining 32% of the white and 12% of the Bantu volunteers had considerably raised levels, but these finally returned to the low base levels after 32 weeks. The more rapid return to their base levels by the majority of the Bantu is probably due to the similarity between this diet and that to which they are naturally accustomed; one would expect that they would readily adapt to this diet. The white volunteers, on the other hand, who are naturally accustomed to a high-fat-caloric intake have to adapt to a less familiar diet.

The slow return to their base levels by almost a third of the white volunteers may relate to the observation in our previous study that the older white male population was not homogeneous, different sections showing different age trends as indicated by the significant increase in standard deviation with increasing age. This seems to lend further support to the implication that the older overtly normal population consists of a mixture of true normals with a large proportion of subjects who may represent potential ischæmic-heart-disease cases.

Before the increase in the proportion of fat calories, volunteers of both races had subsisted for at least a year on a low fat diet, and their mean fasting serum-triglyceride

levels were low. Even after about 2 years on high-fat-calorie diets which raised the serum levels for considerable periods, all levels had returned to the low base values within about 6 months of the low-fat-calorie diet being reinstituted. Since both groups again had low fasting serum-triglyceride levels, it is apparent that low-fat diets, which may temporarily elevate serum-triglyceride levels, eventually reduce values that have been raised through habitual consumption of high-fat foods.

This aspect of the trial clearly shows that it is important to consider the previous dietary history before changes in dietary habits are recommended, since it is possible, by curtailing the proportion of dietary fat, to increase previously raised serum-triglyceride levels temporarily even more before the values are lowered. In view of recent work which indicates a close relation between hyperlipæmia and accelerated blood-clotting and decreased blood-fibrinolytic activity, the production of even temporary lipæmia may be inadvisable in ischæmic-heart-disease patients.

Summary

White and Bantu subjects, when habituated to a particular diet, had fasting serum-triglyceride levels not significantly different, the composition of the fatty-acid components being almost identical; furthermore, both groups responded in the same way to dietary manipulation.

After habituation to a low-fat-calorie diet, the consumption of a high-fat-calorie diet rich in monoenoic and saturated fatty acids for a year resulted in a significant rise of previously low serum-triglyceride levels. Change from high-fat to low-fat diets also produced significantly temporary increase of serum-triglyceride levels, which only returned to base levels after 3–6 months. Fasting serum-triglyceride fatty-acid composition strongly resembled that of the dietary fat.

It is suggested that the nature and proportion of fat in the diet may influence the rate of clearance of triglycerides from the blood-stream, thereby affecting fasting (residual) serum-triglyceride levels.

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PLASMA-IRON AND HÆMOGLOBIN LEVELS IN PREGNANCY

The Effect of Oral Iron

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IN normal pregnancy, the blood-hæmoglobin level usually falls because the plasma-volume increases faster than the mass of the red cells (Dieckman and Wegner 1934, Thomson et al. 1938, Roscoe and Donaldson 1946, Berlin et al. 1953, Gemzell et al. 1954). The fall in hæmoglobin level can be diminished by giving iron to the pregnant woman (Scott and Govan 1949, Klopper and Ventura 1951, Benstead and Theobald 1952, Holly 1954, Kerr and Davidson 1958). Treatment with iron during pregnancy may also raise the mean corpuscular hæmoglobin concentration (M.C.H.C.), even though initially it was within the normal range (Benstead and Theobald 1952).

Further evidence for the occurrence of iron deficiency in pregnancy has been provided by studies of iron metabolism. A fall in plasma-iron, a rise in plasma total iron-binding capacity (T.I.B.C.) (Laurell 1947, Fay et al. 1949, Holly 1954), and an increased efficiency of iron absorption (Hahn et al. 1951) have been demonstrated. These changes are similar to those found in iron-deficiency anæmia. More recently it was shown (Sturgeon 1959, Verloop et al. 1959) that women who were treated with iron (oral or parenteral) during pregnancy had higher plasma-iron values and lower T.I.B.C. at term than women who received no supplemental iron. Hence there is both hæmatological and biochemical evidence that the anæmia of pregnancy is, at least in part, due to iron deficiency.

The incidence of anæmia in pregnancy varies greatly in different countries, and in different economic groups within the one population (Strauss and Castle 1932, Fullerton 1936, Doyle and McGrath 1954). In a previous study of pregnant women in Australia, a fall in mean hæmoglobin level from 13·26 g. in the third month of pregnancy to a minimum of 12·10 in the eighth month, followed by a rise to 12·22 in the tenth month, was observed (Walsh et al. 1953). These workers also noticed that in women who had received iron during pregnancy the mean hæmoglobin levels were similar to those of women given no iron. In the last month of pregnancy the incidence of hæmoglobin values below 10·05 g. per 100 ml. was 3%, this being much less than the incidence observed in other countries. It thus appears that the Australian woman may be in a better state of iron nutrition than women elsewhere.

This paper records the changes in certain hæmatological values, in plasma-iron, and T.I.B.C. during normal pregnancy in another Australian population group. The effect of oral iron administration at different stages of pregnancy was also investigated.

Material and Methods

Plan of Study

All patients attending two different antenatal clinics at the King Edward Memorial Hospital for Women, Subiaco, Western Australia, during a period of six months were included in this investigation. Those attending one clinic received no treatment (control group), while those attending the other received ferrous gluconate and were

* This work was begun while employed as a resident medical officer, Department of Biochemistry, Royal Perth Hospital.

advised to take one 0·3 g. capsule three times daily (100 mg. Fe^{++} per day) from their first antenatal visit until parturition. Attendance at one or the other clinic depended only upon which day of the week the patient chose for her regular monthly visit to the hospital. The date of the last normal menstrual period was used to calculate the stage of pregnancy.

At the first antenatal visit, and at one or two other visits during pregnancy, the following tests were performed: blood-hæmoglobin level and hæmatocrit value, plasma-iron and T.I.B.C., and examination of a blood-smear. At each visit the women who were receiving ferrous gluconate were asked whether they were taking the tablets regularly. 234 women who received no iron, and 122 who took supplemental iron, were studied.

Laboratory Methods

The blood was collected between 9 A.M. and 11 A.M. from the antecubital vein. The women were not fasting. Hæmoglobin was measured photometrically as the oxy-derivative using a Gallenkamp photoelectric colorimeter with a yellow-green filter (Ilford no. 625) and a neutral-grey density screen. The instrument was calibrated and checked regularly with standard blood samples of known hæmoglobin value, supplied for this purpose by the New South Wales Red Cross Blood Transfusion Service. Wintrobe hæmatocrit tubes, 10 cm. long, were used for the hæmatocrit determination. They were centrifuged at a force of 1400 g. for thirty minutes. Blood-films were stained by the May-Grünwald-Giemsa technique recommended by Dacie (1956). Plasma-iron and plasma T.I.B.C. were estimated by a method described by Morgan and Carter (1960).

TABLE I—CONTROL GROUP. HÆMOGLOBIN, MEAN CORPUSCULAR HÆMOGLOBIN CONCENTRATION, PLASMA-IRON, AND PLASMA TOTAL IRON-BINDING CAPACITY LEVELS IN NORMAL PREGNANCY. NO SUPPLEMENTARY IRON GIVEN. MEAN VALUES AND OBSERVED RANGE GIVEN FOR EACH FOUR-WEEK PERIOD OF PREGNANCY

Weeks pregnant	No. of patients	Hæmoglobin (g. per 100 ml.)	M.C.H.C.	Plasma-iron (µg. per 100 ml.)	T.I.B.C. (µg. per 100 ml.)
5–8	7	13·5 (*13·1–14·1*)	32·8 (*31–35*)	123 (*74–161*)	332 (*242–396*)
9–12	19	13·7 (*12·1–15·2*)	33·0 (*31–35*)	123 (*53–172*)	387 (*285–478*)
13–16	26	13·1 (*10·8–15·3*)	33·1 (*31–35*)	109 (*24–178*)	390 (*304–548*)
17/20	33	13·0 (*11·1–14·5*)	33·1 (*30–36*)	114 (*24–180*)	404 (*230–634*)
21–24	29	12·9 (*10·1–15·0*)	33·3 (*30–36*)	98 (*20–274*)	427 (*294–594*)
25–28	25	12·8 (*10·4–14·8*)	33·6 (*31–35*)	81 (*24–156*)	493 (*368–674*)
29–32	40	12·4 (*10·7–14·9*)	33·5 (*31–37*)	97 (*54–185*)	497 (*264–706*)
33–36	36	12·9 (*10·9–16·4*)	33·2 (*30–36*)	96 (*26–170*)	540 (*373–706*)
37–40	27	12·7 (*10·8–14·6*)	32·8 (*30–36*)	93 (*22–186*)	569 (*386–712*)

Results

Table I lists the results of the tests performed on blood from the women receiving no supplemental iron, and table II the results from women who had taken ferrous gluconate for six weeks or more. They have been arranged in four-weekly groups according to the stage of pregnancy at which the estimations were performed. In figs. 1 and 2, the means of these results are shown graphically.

In both treated and untreated women, the mean hæmoglobin value fell progressively during the second trimester and reached a minimum early in the third trimester. During the third trimester, the hæmoglobin rose again in both categories, but the rise was relatively greater in the group receiving supplemental iron. In this group the mean hæmoglobin level was as high during the last month of pregnancy as it was during the first three months. The difference in hæmoglobin level found between treated and untreated subjects in the last month of pregnancy was statistically significant ($P < 0·01$).

TABLE II—IRON-SUPPLEMENTED GROUP. HÆMOGLOBIN, M.C.H.C., PLASMA-IRON AND T.I.B.C. LEVELS IN PREGNANT WOMEN WHO HAD RECEIVED SIX OR MORE WEEK'S SUPPLEMENTARY IRON. MEAN VALUES AND OBSERVED RANGE GIVEN FOR THE LAST SIX FOUR-WEEK PERIODS OF PREGNANCY

Weeks pregnant	No. of patients	Hæmoglobin (g. per 100 ml.)	M.C.H.C.	Plasma-iron (µg. per 100 ml.)	T.I.B.C. (µg. per 100 ml.)
17–20	3	13·4 (*12·9–14·1*)	34·3 (*33–35*)	142 (*89–210*)	350 (*310–408*)
21–24	7	12·7 (*11·6–14·0*)	33·7 (*32–34*)	94 (*76–130*)	336 (*262–349*)
25–28	8	12·5 (*10·9–14·3*)	34·1 (*33–35*)	98 (*54–185*)	408 (*332–531*)
29–32	18	12·6 (*10·1–13·8*)	33·6 (*30–35*)	111 (*37–191*)	424 (*269–586*)
33–36	23	13·0 (*11·4–15·1*)	33·6 (*31–35*)	95 (*41–141*)	467 (*356–640*)
37–40	20	13·5 (*11·4–15·3*)	34·2 (*32–37*)	123 (*54–191*)	464 (*352–605*)

The M.C.H.C. was higher at each stage in the group receiving iron than it was in the control group. Although these differences were small throughout, taken over the whole period of observation the difference between group means was significant ($P < 0·05$).

There was no significant difference between the mean plasma-iron values of the two groups, except during the last month of pregnancy ($P < 0·05$). A moderate fall in the plasma-iron occurred during the second trimester in both groups; and a slight rise in the last trimester, in the supplemental group.

The mean plasma T.I.B.C. increased progressively in both groups as pregnancy advanced. In the group treated with iron, however, this rise commenced some three months later (i.e., at about the sixth month of pregnancy). The differences between mean levels in the two groups was highly significant ($P < 0·001$).

Examination of the blood-smears showed no evidence or iron deficiency in any of the patients.

Discussion

Control Group

The changes in the women not receiving an iron supplement were generally similar to those observed by

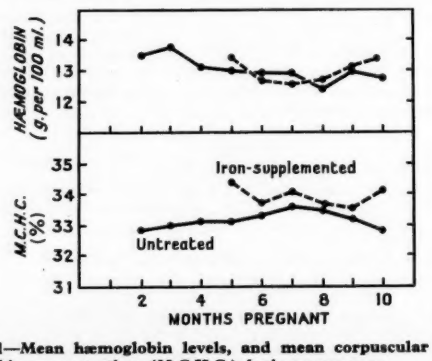

Fig. 1—Mean hæmoglobin levels, and mean corpuscular hæmoglobin concentrations (M.C.H.C.) during pregnancy.

the majority of other workers. However, the decrease in hæmoglobin level was small when compared with other reports. This, and the absence of any patients with hæmoglobin levels below 10 g. per 100 ml. blood in a group of almost 250 pregnant women, is a noteworthy observation. Our results are similar to the results of Walsh et al. (1953). This probably indicates that the iron status of Australian women of childbearing age is generally good.

In table III are shown the mean plasma-iron and T.I.B.C. levels for the last five months of pregnancy arranged according to whether the corresponding hæmoglobin level was below 12·0, 12·0 to 13·0, or greater than 13 g. per 100 ml. A high degree of correlation between plasma-iron and hæmoglobin levels is apparent from the table. This was confirmed statistically. The correlation coefficient for this relationship is 0·30 ($P < 0.001$). A similar observation with regard to plasma-iron and hæmoglobin levels during pregnancy has been made by Holly (1954). No significant correlation between hæmoglobin level and T.I.B.C. could be demonstrated from the results.

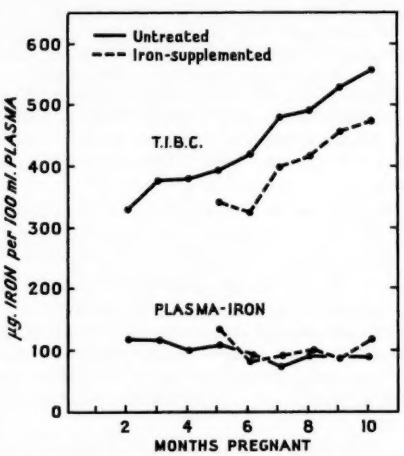

Fig. 2—Mean total iron-building capacity (T.I.B.C.), and plasma-iron levels during pregnancy.

Iron-supplemented Group

Iron administration during pregnancy resulted in a highly significant reduction in the mean plasma T.I.B.C. compared with the values found in untreated subjects. In addition, the mean hæmoglobin and plasma-iron levels in the last month of pregnancy, or the M.C.H.C. throughout the period studied, were all significantly higher in the iron-supplemented group compared with the corresponding values in the control subjects. The administration of iron to patients with iron-deficiency anæmia produces a fall in T.I.B.C., a rise in hæmoglobin and plasma-iron levels, and in M.C.H.C. Hence the differences found between the control and the treated group were what would be expected on giving iron to iron-deficient patients, and indicated that the changes found in pregnancy were in part due to iron deficiency. This deficiency appears to be slight in the women of the population studied.

A fall in the mean hæmoglobin level was not prevented by the administration of iron. This is true even for those women who had received iron for eleven or more weeks (table IV). Although many workers claim that a "physiological anæmia" does not occur in pregnancy, and that this anæmia is produced by iron deficiency, their claims are mainly based on hæmoglobin estimations performed early in pregnancy and again just before term. Little is known of the changes in the intervening period. The present results indicate that the hæmoglobin level may fall during pregnancy even after prolonged oral iron administration, and that the hæmoglobin level reaches a minimum at about the same stage of pregnancy as it does in women given no iron. This decrease in hæmoglobin level, which is associated with an increase in total hæmoglobin mass, may be better called a pseudoanæmia and it may, at least until further evidence is available, be considered a physiological change.

That supplemental iron should be given to the pregnant woman is widely accepted. The need for supplementation undoubtedly varies considerably amongst different population groups. The present study indicates that the need is not urgent in Australia, but that some improvement can be expected in the mother's hæmoglobin level at term. The pregnant woman at that time has her greatest need for a high hæmoglobin level. Most clinicians agree that the iron should be given orally in the form of one of the many iron salts available. Ferrous sulphate and ferrous gluconate in equivalent doses are equally effective; and unpleasant side-effects are rare (Kerr and Davidson 1958). Table IV shows the blood-hæmoglobin level and plasma T.I.B.C. in the last three months of pregnancy. The results for each month have been arranged according to the duration of iron administration. In general, higher

TABLE III—CONTROL GROUP. MEAN PLASMA-IRON AND T.I.B.C. LEVELS ARRANGED ACCORDING TO CORRESPONDING HÆMOGLOBIN LEVEL

Weeks pregnant	Hæmoglobin (g. per 100 ml.)	Number of patients	Plasma-iron (μg. per 100 ml.)	T.I.B.C. (μg. per 100 ml.)
21–24	12·0	4	78	381
	12·0–13·0	9	96	415
	13·0	16	107	443
25–28	12·0	3	41	542
	12·0–13·0	12	73	482
	13·0	10	102	492
29–32	12·0	13	98	510
	12·0–13·0	18	96	489
	13·0	9	89	524
33–36	12·0	11	83	541
	12·0–13·0	11	83	557
	13·0	14	109	542
37–40	12·0	8	70	552
	12·0–13·0	9	82	583
	13·0	10	121	578

TABLE IV—IRON-SUPPLEMENTED GROUP. MEAN BLOOD-HÆMOGLOBIN AND PLASMA T.I.B.C. LEVELS IN PREGNANT WOMEN, ARRANGED ACCORDING TO THE DURATION OF SUPPLEMENTARY IRON ADMINISTRATION

Weeks pregnant	Duration of iron supplementation (weeks)	Number of patients	Hæmoglobin (g. per 100 ml.)	T.I.B.C. (μg. per 100 ml.)
25–28	Nil	25	12·8	493
	1–5	9	12·3	408
	6–10	5	12·2	417
	11 or more	3	12·9	399
29–32	Nil	40	12·4	497
	1–5	12	12·3	488
	6–10	9	12·4	466
	11 or more	9	12·7	381
33–36	Nil	36	12·9	540
	1–5	14	12·4	482
	6–10	8	12·9	495
	11 or more	15	13·1	450
37–40	Nil	27	12·7	569
	1–5	6	12·8	500
	6–10	9	13·7	476
	11 or more	11	13·3	455

hæmoglobin levels were observed in those women who received iron for the longer periods than in those women not given iron, or given it for less than six weeks. The duration of iron therapy had more effect on T.I.B.C. than on hæmoglobin level. Almost without exception, in each four-week group, the longer iron was administered, the more the mean T.I.B.C. fell. These results therefore suggest that, for maximum benefit, supplemental dietary iron should be given for a period of at least three months. Possibly the best plan would be to administer the iron from some time in the second trimester until term.

The mechanism regulating the T.I.B.C. of the plasma is unknown. An increase is observed in pregnancy and in iron deficiency. My finding that the rise during pregnancy can be diminished by iron administration, but cannot be eliminated, agrees with that by Sturgeon (1959) and Verloop et al. (1959). Sturgeon treated one group of women with intramuscular iron with a mean dose of 943 mg. iron—a dose sufficient to meet the demands of the fœtus and of the mother's own increase in hæmoglobin mass. Even so, an increase in the mean T.I.B.C. from 347 in early pregnancy to 475 at term was observed. As stated earlier, the efficiency of iron absorption is increased in pregnancy. It is likely that our patients treated with oral iron were able to absorb sufficient iron for their needs, and their iron status was no worse than Sturgeon's patients treated with parenteral iron. This assumption is supported by the observation that the reduction in mean T.I.B.C. in the group treated with oral iron was very similar to that found by Sturgeon with parenteral iron. Further evidence that the rise in T.I.B.C. in pregnancy is, in part, due to some factor other than iron deficiency is, provided by the observations of Gerritsen and Walker (1954) who found that the T.I.B.C. rises in pregnancy in Bantu women. Owing to dietary habits, the body-iron stores of the Bantu are considerably larger than those of Western peoples.

Summary

Changes in blood-hæmoglobin level, mean corpuscular hæmoglobin concentration (M.C.H.C.), plasma-iron, and total iron-binding capacity were studied in two groups of pregnant women. One group received iron as ferrous gluconate and another comparable group received none. Throughout pregnancy iron administration reduced the mean total iron-binding capacity, and increased in M.C.H.C. Compared with the untreated women, no difference was found for plasma-iron or blood-hæmoglobin levels until the last month of pregnancy, when both values were higher in the treated than in the untreated groups.

The iron status of the women studied, the need for iron supplementation during pregnancy and the duration of such treatment, the meaning of the term "physiological anæmia" of pregnancy, and the cause of the changes observed in plasma iron-binding capacity are discussed in the light of the results.

I am grateful to Prof. G. King, Dr. R. Nattrass, Mr. G. H. Vos of the King Edward Memorial Hospital for Women, and to Dr. D. H. Curnow of the Royal Perth Hospital, for their cooperation throughout this investigation. The hæmatological tests were performed by the department of hæmatology, Royal Perth Hospital. Mr. N. Stenhouse of the division of mathematical statistics, C.S.I.R.O., Perth, undertook the statistical analyses. Dr. I. Kaldor, department of physiology, University of Western Australia, provided most valuable advice and criticism during preparation of this paper.

References at foot of next column

DELAYED AND LONG-LASTING ELECTROCARDIOGRAPHIC CHANGES IN CARBON-MONOXIDE POISONING

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WHEN death has been caused by carbon-monoxide poisoning, the pathological changes in the heart usually resemble those found in any death from anoxia.

The earliest report appears to be that of Klebs (1865), who described punctiform and diffuse hæmorrhages in the pericardium and in the tips of the papillary muscles. Gürrich (1926) and Fishberg (1940) made similar observations. Gürrich described hæmorrhagic and necrotic foci, surrounded by leucocytic infiltration, scattered throughout the heart, especially in the septum and papillary muscles. The changes in the electrocardiograms (E.C.G.s) of patients exposed to anoxia were first described in the early 1920s by Greene and Gilbert (1921) and Haggard (1921); and later Colvin (1928) and Steinmann (1937) reported these findings in carbon-monoxide narcosis.

Anoxic changes in the ST segment of the E.C.G.—i.e., depression of the RT segment and inverted T waves—have been described, and are usually considered ephemeral. Abnormalities of rhythm and conduction are found, but not often enough to support the contention of some workers that the anoxia acts first on the more highly specialised tissue, such as the conducting tissue. Carbon monoxide is usually thought to exert its effects by the preferential formation of carboxyhæmoglobin giving rise to tissue anoxia.

Coal-gas poisoning is a common accident, and it was the method used in thirty out of two hundred attempted suicides reported in this group of hospitals within a 5-year period. Accordingly we felt that delayed and long-lasting changes in E.C.G.s following exposure to coal gas were worth reporting. Of eleven cases studied in the period July, 1958, to April, 1959, two showed long-lasting changes and two showed more transient ones. Five of the remaining seven patients, who showed no

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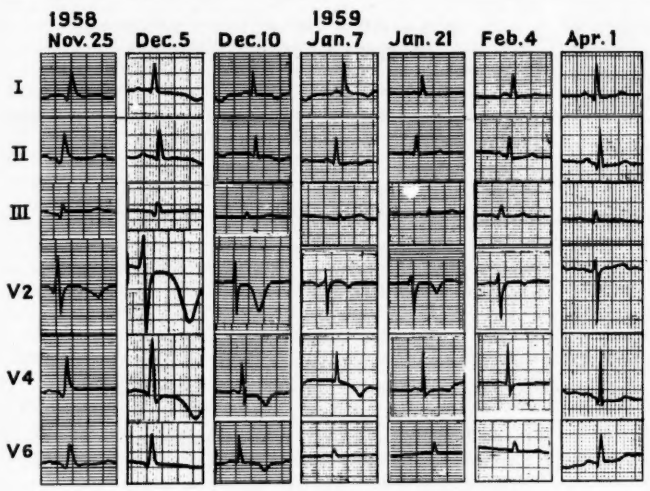

Fig. 1—Serial electrocardiograms of case 1.

initial abnormality, were not kept under observation for more than a week, as they were transferred to a mental hospital.

Case-reports

Case 1.—A woman, aged 40, was admitted as an emergency on Nov. 24, 1958, having been found in a gas-filled room. Length of inhalation of carbon monoxide unknown. This was an attempt at suicide during a reactive depression. Splenectomy, at the age of 10 years, for Gaucher's disease.

The patient was thin, pale, and cyanosed, and was unconscious on admission. Pulse-rate 116 per minute, regular; blood-pressure 150/80 mm. Hg; deep tendon reflexes all brisk and equal; sustained ankle clonus; plantar reflexes, flexor. Carboxyhæmoglobin content of venous blood 23%. Serum-glutamic-oxaloacetic-transaminase (S.G.O.T.) 28 Sigma-Frankel units per 100 ml. Hæmoglobin 14 g. per 100 ml.; white blood-count 13,000 per c.mm.; erythrocyte-sedimentation rate (E.S.R.) 25 mm. in first hour (Wintrobe uncorrected); hæmatocrit value 39%. Chest X-ray normal. Serial E.C.G.s are shown in fig. 1. The patient was given 7% carbon dioxide and oxygen, and intravenous nikethamide. She recovered consciousness in 4 hours, and appeared perfectly well after 24 hours.

Case 2.—A woman, aged 24, was admitted as an emergency at 1 P.M. on Jan. 31, 1959, having been found in a gas-filled room. This was a case of accidental poisoning, the gas main leading to the house having fractured during the night after she and her husband had gone to bed. Length of inhalation of carbon monoxide unknown, but may have been as long as 12 hours, as she said that there was a slight smell of gas when she went to bed.

The patient was a fit-looking young woman of good colour; and, though shivering and unconscious, she responded to painful stimuli. Pulse-rate 100 per minute, occasional extrasystoles. The blood-pressure was 130/80 mm. Hg. No transaminase or carboxyhæmoglobin estimations were made. Hæmoglobin 13·5 g. per 100 ml.; white blood-cells 8000 per c.mm. Chest X-ray normal. Serial E.C.G.s are shown in fig. 2.

Case 3.—Husband of case 2, aged 29. History as that of wife. He was unconscious, but responded to painful stimuli.

Both were given 7% carbon dioxide and oxygen. They recovered in 4–6 hours, and appeared perfectly well after 24 hours.

Discussion

Little has been written about the E.C.G. in carbon-monoxide poisoning, though most textbooks refer to it.

Wood (1956) said that the changes could last for a week or two, and mentioned RST-segment depression and T-wave inversion. Hadley (1952) reported the case of a man who had angina after inhaling exhaust gas (mainly carbon monoxide), and who later died from a presumed coronary thrombosis; the E.C.G. showed ST changes in V_5 and V_6. Hadley also reviewed the work of Haggard (1921) and Steinmann (1937), who showed experimentally that oxygen deficiency led to impaired conduction, affecting the most highly specialised tissues first. Colvin (1928) reported a case in which notching of QRS complex and ST changes were noted in V_{2-6}; these changes had all disappeared by the 13th day. Faivre et al. (1955) reported the cases of two women, aged 52 and 30, who were accidentally poisoned with carbon monoxide. The E.C.G. of the older woman initially showed T inversion, but this had reverted to normal by the 20th day; that of the younger patient was normal throughout.

Both Faivre et al. (1955) and Stearns et al. (1938) refer to the different types of E.C.G. found in carbon-monoxide narcosis: (1) disturbances of rhythm, such as fibrillation and extrasystoles, (2) disturbances of conduction, such as atrioventricular or bundle-branch block, and (3) anoxic changes in the ST segment. Faivre et al. further suggested that carbon monoxide might be a direct myocardial toxin, and that there was individual variation in the response of heart muscle to carbon monoxide. They cited the work of Campbell et al. who showed experimentally that T-wave changes were proportional to increasing concentration of carbon monoxide, or to decreasing concentration of oxygen. The proportion of cases of carbon-monoxide narcosis with some electrocardiographic change is high—twenty-one out of thirty (Steinmann 1937), and twenty-one out of twenty-two (Stearns et al. 1938). In Stearns' series, the length of follow-up was variable—2 weeks or less in fifteen cases. Of the remaining seven, three had normal E.C.G.s on the 22nd, 42nd, and 72nd days; four still showed changes on the 32nd, 39th, 50th, and 66th days.

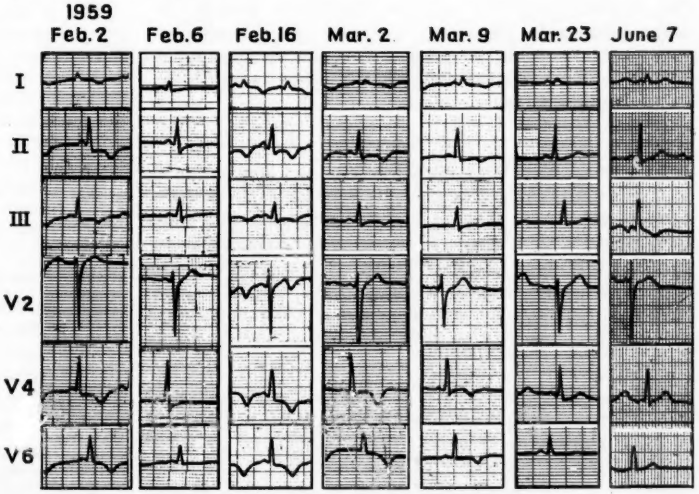

Fig. 2—Serial electrocardiograms of case 2.

The long period—70–100 days—before the E.C.G.s of our patients returned to normal suggests that the myocardium may suffer more than has previously been assumed. We wonder whether these long-lasting changes in the E.C.G. after carbon-monoxide narcosis should affect our management of such cases—for, if there is some degree of long-lasting myocardial damage, should not one suggest a period of partial rest, or, at least, of avoidance of stress?

On the other hand, Jackson (1959) reported T-wave inversion in E.C.G.s of mountain climbers. T-wave changes were recorded in lead V_4 at over 16,000 feet; and persisted, in one instance, for at least 44 hours after the end of a climb to 19,000 feet. Serial studies of S.G.O.T. values in future cases would be interesting, as would an attempt to relate these with the persistence of abnormal E.C.G.s, or their later development.

Case 1 had a splenectomy for Gaucher's disease, and, although the heart and blood-vessels are not affected in this lipid-storage disorder, one may speculate whether this disease could have enhanced the effects of the carbon monoxide. Stearns et al. (1938) comment on the greater degree of change, especially in the conduction mechanism, in one of their cases, in which coronary ischæmia preceded carbon monoxide narcosis.

Case 2 presents several interesting features. The original E.C.G. shows both forms of cardiographic abnormality in response to carbon monoxide—i.e., extrasystoles and ST depression. The extrasystoles disappeared within a week of admission, but returned after 4 weeks. The patient then complained of nervousness, sweating, and tremor. She was found to be thyrotoxic; this was confirmed by high radio-iodine uptake and raised basal metabolic rate. Thyrotoxicosis may have caused the extrasystoles and have led to her increased sensitivity to carbon monoxide. Indeed, there was a striking difference between the E.C.G.s of the patient and those of her husband, though their exposures to carbon monoxide must have been the same, since they were in the same bed. This would confirm the impression of Sayers et al. (1923) that there is an individual variation in sensitivity to carbon monoxide. A further feature of our cases which is difficult to explain is the definite improvement seen in the E.C.G. after a week, and then the even more striking deterioration 3 days later. Some of the statements about the transitoriness of electrocardiographic change in carbon-monoxide poisoning may have been based on the results of too short a period of surveillance. Continued follow-up of a patient after the E.C.G. has become normal or has improved seems advisable.

Summary

Two cases of carbon-monoxide narcosis are reported in which long-lasting changes were seen in serial electrocardiograms taken up to 3 months after exposure. An early return of the electrocardiogram to normal should not preclude continued follow-up.

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A SAMPLE OF BLOOD WITH NO DETECTABLE Rh ANTIGENS

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IN 1950 Race, Sanger, and Selwyn described a blood which failed to react with any Rh antisera except those containing anti-D. The Rh genotype of the person concerned was described as $D--/D--$, and it was considered possible that the C and E portions of the Rh gene complex had been lost by deletion from the Rh chromosome. Since then several other examples of $D--/D--$ have been described, and people whose Rh genotype appears to be DC^w-/DC^w- and $Dc-/Dc-$ have been reported. The genetical background of these groups has been reconsidered recently (Race and Sanger 1960).

In August, 1960, routine testing of blood collected for anthropological purposes from Australian aborigines from the Western Desert revealed a sample which failed to react with the anti-C, anti-D, anti-E, and anti-c sera being used. Further study showed also that it failed to react with anti-e, anti-Ce, and anti-C^w, and also with several other samples of the antisera anti-C, anti-D, anti-E, and anti-c.

A further expedition to the Leonora and Laverton area of Western Australia succeeded in locating the person from whom the blood was originally taken. Fresh samples of blood were brought to Perth, and a sample was flown to the Lister Institute in London for testing with a battery of Rh antisera.

Case-history

Mrs. N. is a full-blood Australian aborigine belonging to a tribal complex inhabiting a region best described as the Western Desert (Berndt 1959). She is 37 and married, but has no living children. Her father, who had no sibs, died when she was an infant, and her mother died recently, aged about 60. Her mother's sibs are dead also. She had only one sib, a sister, who died a few years before she was born. She has, therefore, no close relative alive.

According to tribal rules Mrs. N.'s parents should not be closely related, but in such a small breeding population some consanguinity seems likely; the total population is at present about 2000.

Medical History

Mrs. N. is in normal good health, her only reported sicknesses being pneumonia and influenza. Her mother was

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treated several times during the 7 years before her death for pneumonia, pleurisy, and influenza. The causes of her father's and sister's deaths are not known. She has had three pregnancies. The first, 10 years ago, resulted in a female child which lived about 3 weeks. The second was also a girl, born prematurely at about 32 weeks' gestation, who survived 2 days. The third pregnancy ended in miscarriage at about 3 months' gestation.

Serological Investigations

General.—No abnormalities were seen in the blood film. Electrophoresis of the serum (kindly performed by Dr. C. J. Brackenridge) revealed a pattern not significantly different from that of other aboriginal sera. The haptoglobin type is Hp 2−2, and transferrin type CC. The gamma-globulin groups are Gm(a+b−x−), Gm-like(−).

Mrs. N.'s groups are A_1, *Ns/Ns*, P_1, Lu(a−b+), K−k+ Kp(a−b+), Le(a−b+), Fy(a+b−), Jk(a+b+). Her cells reacted positively with 13 antisera to "public" antigens (amongst them were anti-Vel, anti-Yt^a, anti-Ge, and anti-I), and negatively with 24 antisera to "private" antigens.

Rh tests.—The red blood-cells were tested in Perth and in London against many Rh antisera using saline, albumin, Löw's, ficin, or anti-globulin methods depending on the nature of the particular antiserum. Her cells failed to react with the following sera: 25 anti-D, 13 anti-C+D (+G), 13 anti-C (including some mainly of the specificity anti-Ce and one mainly of the specificity anti-CE), 2 anti-C^w, 1 anti-C^x, 10 anti-E, 1 anti-E^w, 3 anti-c+E, 14 anti-c, 14 anti-e, 2 anti-f (anti-ce), 2 anti-G, 2 anti-V (anti-ce^s), 2 anti-VS (anti-e^s), 5 sera from immunised *D−−/D−−* persons, 1 from an immunised *DC^w-/DC^w-* person, 2 from immunised *Dc−/Dc−* persons (these last 8 sera have reacted with all random samples tested, but not with their own or each other's cells), and with 7 sera from immunised Negroes who have made antibody not unlike anti-e.

In one absorption experiment Mrs. N.'s cells did not remove any antibody from an anti-D serum nor from the serum of an immunised *D−−/D−−* person, whereas absorption by control *cDE/cde* cells caused much reduction in antibody.

In a second absorption experiment the cells and control *CDe/cDE* cells were incubated separately with anti-C, anti-D, anti-E, anti-c, and anti-e, and eluates were prepared from the cells, after incubation, by a slight modification of the method of Vos and Kelsall (1956). In each case antibody was present in the eluate from the control cells, but no antibody was detectable in any of the eluates from Mrs. N.'s cells. Absorption and elution tests therefore confirmed the negative agglutination tests.

No Rh antibody of any kind could be found in Mrs. N.'s serum.

Discussion

Mrs. N. is the only person so far reported whose red blood-cells completely fail to react with any known Rh antiserum. The lack of living relatives is unfortunate: tests on the blood of her family might have given some clue to the genetic basis of her entirely negative Rh phenotype.

The phenotype may reflect the absence of a very frequent gene necessary for the production of some Rh precursor substance. A precedent is the *X* gene (of Levine et al. 1955) in the absence of which the *ABO* genes cannot express themselves as antigens.

Alternatively, deletion may be responsible. The deletion would presumably have to be a short one, for Mrs. N. is normal in other respects. The possibility of deletion of the whole Rh-gene complex was postulated by Henningsen (1958): he interpreted two mother-child Rh inconsistencies in one family as being due to heterozygosity for a complete Rh deletion. In the remote possibility that a visible deletion may be responsible we are trying to arrange for the karyotype of Mrs. N. to be investigated. If any abnormality were detected not only would the phenotype be explained but, more important, the Rh locus could then be assigned to a numbered chromosome and a beginning would have been made of the mapping of the human autosomes.

The condition may, of course, have a more complex background: Race and Sanger (1960) have given reasons for thinking that more than one gene may be involved in the *D−−* complex.

In the absence of relatives we are left with no clue to the genetic background of Mrs. N.'s $--\frac{-}{-}/---$ condition. We hope that further examples may be found in the tribal complex to which she belongs: so far about 450 of the 2000 members of the tribe have been tested.

Summary

The blood of an Australian aborigine has been found to lack all of the known Rh antigens.

We are indebted to the Western Australian Department of Native Welfare for their cooperation in facilitating our studies of aborigines, and particularly to Mr. J. Beharell and Mr. D. Hardwick for their invaluable assistance in helping us to locate and to make contact with Mrs. N. We are also grateful to Mr. Wilfred Douglas, aboriginal language expert of the United Aborigines Mission, who collected the detailed genealogical information for us.

The research grants committee of the University of Western Australia and the Australian National Health and Medical Research Council provided financial assistance to one of us (R. L. K.), which made the collection of specimens of blood from Mrs. N. possible. We are indebted also to the medical superintendent of the King Edward Memorial Hospital for permission to publish these results.

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BASILAR ARTERY MIGRAINE

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> If darkness possess the eyes, and if the head be whirled round with dizziness, and the ears ring as from the sound of rivers rolling along with a great noise, or like the wind when it roars among the sails, or like the clang of pipes or reeds, or like the rattling of a carriage, we call the affection Scotoma (or vertigo) . . . The mode of vertigo is heaviness of the head, sparkles of light in the eyes along with much darkness, ignorance of themselves and those around, and if the disease go on increasing, the limbs sink below them and they crawl on the ground; there is nausea and vomiting of phlegm, or of yellow or black bilious matter.
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> ARETÆUS (circ. A.D. 100).

THOUGH migraine is one of the commonest disorders encountered in medical practice, the exact way in which the symptoms are produced has not been established to the complete satisfaction of all. The most probable explanation is that the headache is due to excessive dilatation of extracranial and dural vessels, and that in many this is preceded by constriction of certain intracranial cerebral vessels resulting in transient ischæmia in the territory of these vessels, with the production of the familiar aura. Thus, constriction of ophthalmic or retinal vessels can produce unilateral loss of vision, altitudinous field defects, or various scotomata; involvement of vessels to the chiasma causes bitemporal hemianopia or "blinker vision"; and, if the middle cerebral artery is involved, there are unilateral paræsthesiæ of [illegible]hand, and arm. There may even be weakness of one

arm; and, if on the dominant side, there may be alarming dysphasia.

All these symptoms are referable to branches of the internal carotid artery, but some prodromal symptoms cannot be explained in this way. The positive ill-formed visual hallucinations in homonymous fields at times closely resemble those produced by structural lesions of the occipital lobe, and some of the hemianopic manifestations are almost certainly due to involvement of the posterior cerebral artery. This, however, is the territory not of the internal carotid, but of the basilar artery; and there seems no reason why, if one branch of this vessel should often be involved, others—or even the main vessel itself—should not be involved as well. The premonitory symptoms would be different and would reflect brain-stem dysfunction or, if the upper part of the basilar artery at its division into posterior cerebrals is affected, dysfunction of both occipital cortices.

This paper is intended to show that this may be so in migraine, and a clinical syndrome may be produced which, though unfamiliar to many clinicians, is not particularly rare.

The material is drawn from a personal series of 300 patients in whom the clinical diagnosis of migraine seemed justifiable. All the patients were asked to give as exact an account as possible of their prodromal symptoms, and were urged to clarify such vague terms as " giddiness ", " black-outs ", or " unsteadiness " which have such different meanings to different persons. In this way, 34 patients were discovered whose clinical symptoms suggested involvement of the basilar system in greater or lesser degree.

Case-reports

Case 1.—A 13-year-old girl had had four menstrual periods, and three days after the end of each had had an attack in which she experienced vivid flashes of light throughout the whole visual field in both eyes. These flashes were sufficiently intense to obscure her vision completely. At the same time she had tingling in both hands and both feet, and her speech became so slurred as to be barely intelligible. She then became ataxic on attempting to walk. These symptoms lasted fifteen minutes and then subsided, and were followed by severe throbbing occipital headache and vomiting. After vomiting, she felt better, and would sleep for several hours and awaken free from headache.

Her father and an aunt had severe migraine.

Electroencephalograms (E.E.G.s) were normal, and treatment with prochlorperazine during the postmenstrual week has relieved her of these symptoms for six months.

Case 2.—A 13-year-old girl first menstruated at the age of 12, since when she has had frequent attacks of headache. Each attack is preceded by severe rotational vertigo, during which her gait becomes so ataxic that she has to lie down. She then loses her vision completely in both eyes for " as long as it takes to count seven ". This total loss gives place to generalised dimness of vision which lasts half an hour, and then normal vision returns; and after an interval she has severe occipital headache, which has several times been accompanied by vomiting. After about an hour she feels better and sleeps. She has had several other attacks in which the premonitory symptoms were loss of vision in homonymous fields, but this might be on either side on different occasions. Nothing abnormal was found on examination.

Case 3.—A 14-year-old girl had been subject for three years to attacks in which vivid flashes of light, developing in both visual fields, would last for fifteen minutes and would be followed by retro-orbital headache lasting an hour. During one of these attacks the flashes of light became so severe as to obscure her vision completely; at the same time she became unsteady on her feet, and rotational vertigo developed. These symptoms lasted about thirty-five minutes, and she then had a severe throbbing occipital headache which persisted for several hours. Her mother had severe migraine.

X-rays of the skull, cerebrospinal fluid (C.S.F.) examination immediately following this severe attack, and E.E.G.s were normal.

Case 4.—A boy of 14 was walking quietly down a street when he realised that the vision was failing in both eyes, and within fifteen seconds he was blind. At the same time he had rotational vertigo and became extremely ataxic. He then had intense paræsthesiæ of both hands and both feet, and his speech became slurred. After ten minutes the vision began to return, and in fifteen minutes these symptoms had disappeared; but an intense throbbing occipital headache developed which lasted for two hours, during which time he vomited. He then slept for a while and awoke entirely normal. He had had three attacks of this type, in between each of which he had been free from all symptoms, and had had several other attacks of teichopsia followed by throbbing headache. There was a strong history of migraine in his family. Examination, X-rays of skull, E.E.G.s, and C.S.F. examination were all normal.

The Clinical Syndrome

Age.—Of the 34 patients who had this syndrome to greater or lesser degree, all but 2 were under the age of 23. All were under 35.

Sex.—26 of the 34 patients were adolescent girls.

Family history.—A clear-cut history of migraine in close relatives was obtained in 28 cases.

Onset.—The first symptom was usually visual; in some this consisted of total loss of vision, and in others of positive visual manifestations throughout both visual fields, usually so intense as to obscure vision. This was followed by vertigo, ataxia of gait, dysarthria, and occasionally tinnitus—not necessarily in that order, and the ataxia was not necessarily associated with vertigo. Sensory manifestations consisted in tingling or numbness in the periphery of both hands and both feet, and sometimes around both lips and on both sides of the tongue.

Course.—These symptoms lasted from two minutes to a maximum of forty-five and then subsided rapidly, though, if there had been complete loss of vision, this disappeared more gradually (five minutes) through a period of greying of vision.

The headache.—In each case the disappearance of the premonitory symptoms was accompanied by severe throbbing headache, usually in the occipital region, and often accompanied by vomiting. This appeared to relieve the headache, which finally ceased when the patient slept.

Frequency of attacks.—These attacks were infrequent, but in the girls were strikingly related to menstruation. In between these attacks many patients had more classical migrainous episodes. Over the years there is a tendency for this type of attack to cease and to be replaced by the more common variety.

Treatment.—Simple use of regular prophylactic phenobarbitone is effective, and prochlorperazine taken regularly appears to give relief in the older children.

Discussion

A diagnosis of migraine is impossible to prove. In these cases, however, the mode of onset, with the associated headache, the relatively brief duration of the attack, the family history of migraine, the occurrence of other attacks more typically migrainous, and the absence of all abnormalities in between attacks makes the diagnosis of some transient vasomotor disorder highly probable. Some of these patients may conceivably have had angiomata in the brain-stem, but none has had any hæmorrhagic manifesta-

tion—and some have now been kept under observation for six years—while the rapid return to complete normality after each attack argues against structural disease. 2 patients had vertebral arteriograms carried out which were normal.

The general public are familiar with the classical symptoms of migraine; the medical profession have learned to recognise the more alarming dysphasias and unilateral dysæsthesiæ; but the sudden development of signs of brain-stem disorder in a young person is alarming to all, and not unnaturally the presence of a posterior-fossa tumour is feared. Stress should be placed on the sequence of events described, and three important features are: (*a*) the occurrence of other more classically migrainous attacks at other times; (*b*) the return to complete normality in a short time; and (*c*) the family history.

These cases are florid examples of the disorder, but involvement of the basilar system is probably commoner than is appreciated, since vertigo is a common feature of migrainous episodes, and many patients—particularly the older ones—emphasise the sense of instability during their attacks. Probably, in an attack of migraine, the territory of several vessels may be involved; but, in any given attack, one vessel is predominantly affected and, according to its site, certain symptoms may be dramatic enough to obscure others from the patient's mind, and so from the history.

Finally, the headache following this type of attack has much more commonly been occipital than either generalised or hemicranial, and it seems that the site of maximal extracranial vascular distension is influenced in some way by the site of the initial intracranial vasomotor disturbance.

Why this syndrome is found predominantly in adolescents is not clear; but, though there may be some hormonal influence, it may simply reflect the instability of vasomotor control at this particular age.

Summary

Though most of the familiar premonitory features of an attack of migraine can be explained on the basis of a vasomotor disturbance in the territory of the internal carotid artery, in some cases signs of brain-stem dysfunction predominate.

Symptoms consist in bilateral loss or disturbance of vision, ataxia, dysarthria, vertigo, tinnitus, and bilateral peripheral dysæsthesiæ, followed by occipital headache.

The syndrome is commonest in adolescent girls.

It may represent a migrainous disturbance affecting the basilar artery system.

"... The Soviets claim, time and again, that their type of society which has a clear-cut, well-defined goal and a collectivistic orientation in its culture, leads to a lesser degree of mental illness than a capitalistic society with its antagonistic classes, its violent competition, its irresponsible individualism, and its multiplicity of goals. ... If there is an inverse relationship between common goals or culture and mental illness, it is perhaps in the area of neuroses where it will be most evident. ... The present approach to the neuroses is that they are the results of bad social conditions or traumatic events (such as war or unemployment) and that with an increase in the welfare and the security of the population they are bound to disappear. It is perhaps this approach to the neuroses that makes it so difficult for Soviet medical and lay authorities to understand certain social problems that plague Soviet society. Juvenile delinquency, crime and alcoholism are examples of such problems. ... Nor is it easy for Soviet psychiatrists to understand why, in the United States, there are so many neurotics in the upper socio-economic groups of the population."—MARK G. FIELD, PH.D., *Social Problems*, 1960, **7**, 277.

THREE AMINE-OXIDASE INHIBITOR DRUGS IN THE TREATMENT OF DEPRESSION

Relative Value and Toxic Effects

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AT St. George's Hospital, an outpatient clinic for the treatment of depressed patients with the new antidepressant drugs was started in July, 1959. At first, the only drug used was imipramine (' Tofranil ') and the results obtained tallied with those reported elsewhere (Ball and Kiloh 1959, and others). The best results were obtained in endogenous depressions, but we were impressed by the sometimes quite serious complications—e.g., severe hypomanic reactions, the apparent precipitation of a serious suicidal attempt, a hallucinatory episode, and several cases of male impotence. These were in addition to the commonly described physical side-effects—such as sweating and skin eruptions. When the drug was going to be effective, the benefits were usually apparent within five to ten days.

We were chary of trying the early amine-oxidase-inhibitor drugs because there were reports of severe liver damage with iproniazid; but, as more drugs became available, we decided to try three of them, since the new and sensitive tests would probably detect early liver damage.

Design of Trial

The drugs used in the trial were iproniazid (' Marsilid '), nialamide (' Niamid '), and pheniprazine (' Catron '). All are amine-oxidase inhibitors; their respective side-effects are not specific enough for their identification.

Our procedure was to increase the dose, if necessary, beyond that recommended so long as there was no evidence of liver damage. To ensure safety, a pilot trial was instituted on inpatients. Later, we gave these drugs to patients who were referred to the clinic previously devoted to treatment with imipramine. About three-quarters of the patients were suffering from endogenous or involutional depressions; the rest had reactive depressions or depressive states associated with personality disorder. All patients were seen and assessed by one of us (A. H. C.), whilst another (P. H.) took the blood for liver-function tests and prescribed one of the three drugs. Precautions were taken to ensure that neither knew the other's decisions about precise symptomatic alteration or drug prescribed. The drug was randomly selected, and the laboratory form stated only that the patient was receiving antidepressive medication. The trial was therefore blind.

17 courses of iproniazid, 18 of nialamide, and 20 of pheniprazine were given from which the results were complete enough to allow their inclusion for analysis. One patient received 2 courses for two separate attacks of endogenous depression; some patients were treated successively with more than one drug.

Dosage

Initially, iproniazid was given at 50 mg. three times daily, nialamide at 50 mg. three or four times daily, and pheniprazine at 3 mg. four times daily. The assessor would indicate to the

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TABLE I—CLINICAL RATINGS OF AMINE-OXIDASE INHIBITORS

—	Mean initial depression rating	Mean final depression rating	Mean differences
Iproniazid	22·6	13·6	9·0
Pheniprazine	24·7	13·7	11·0
Nialamide	24·7	15·4	9·3

prescriber when he thought that an increased dosage was desirable, or when he thought that improvement was convincing enough to allow of reduction of the drug with a view to ultimate withdrawal. The point at which the standard dose was reduced was later taken to mark the end of the trial period of that particular patient. If no improvement had taken place after about six weeks, the point when the drug was stopped was taken to be the end of the trial period.

Results

Clinical ratings.—A rating scale was constructed, based on numerical assessment (0–6) of each of the following: mood, reactivity, agitation, psychomotor output (subdivided), appetite, sleep, and mental content. Thus, a patient psychiatrically well in all these respects would score 0, whilst one with a moderately severe depression might score a total of 25–35 out of a possible 48.

Table I summarises these results. There was no significant difference in the mean initial depression rating among the three groups. The improvement in depression rating was the same for iproniazid and nialamide, while the differences between pheniprazine and the other two drugs were not significant.

Liver-function tests.—After a preliminary survey, the battery of liver-function tests used was narrowed down to serum-glutamic-oxaloacetic transaminase (S.G.O.T.), serum-glutamic-pyruvic transaminase (S.G.P.T.), thymol turbidity, and serum-bilirubin. Jaundice is said to be predictable on the basis of a rising transaminase level during treatment with iproniazid (Pare and Sandler 1959) and we thought that the same warning would probably be given by other amine-oxidase inhibitors.

All patients were rated for depression at each visit, and blood was taken for liver-function tests; a sharp fall in depression rating, a rise in transaminase values, or sudden change in the results of the other liver-function tests were signals for reduction or cessation of the drug being given.

Table II summarises the results of the series giving the mean differences between initial and final measurements

TABLE II—EFFECT OF AMINE-OXIDASE INHIBITORS ON LIVER-FUNCTION TESTS

—	S.G.O.T.	S.G.P.T.	Serum-bilirubin	Thymol turbidity
Iproniazid	3·6*	13·23*	0·04	0·08*
Pheniprazine	0·25	1·25	0·05	0·15*
Nialamide	0·17*	2·33*	0·01	0·11

* Indicates a deterioration of liver function.

of the liver-function tests expressed in terms of their respective units of measurement.

The mean difference between initial and final measurements of S.G.O.T., serum-bilirubin, and thymol turbidity for the three drugs did not differ significantly. The difference, however, between the initial and final S.G.P.T. values of the group of patients taking pheniprazine and of those taking iproniazid was significant ($0{\cdot}02 > P > 0{\cdot}01$). Nialamide was not significantly different from iproniazid.

We had originally supposed that the differences in toxicity, if any, would have to be set against differences in therapeutic effect (at an arbitrary dosage); but the order of efficacy (in these artificially restricted circumstances) proved to be the reverse of the order of toxicity; so in fact the toxic effects could be compared directly.

Summary and Conclusions

In a special outpatient clinic depression was treated with the new antidepressive drugs, including imipramine, iproniazid, nialamide and pheniprazine.

Some general impressions gained while using these drugs were: (1) in endogenous depression amine-oxidase inhibitors seem to be almost as effective as imipramine, each being of considerable benefit in over half the cases. With imipramine the response seemed to be more all-or-none. In depressions other than those classically endogenous the amine-oxidase inhibitors seemed to have a better effect than imipramine; and (2) in long-standing depressions or in those affecting older people, the amine-oxidase inhibitors seemed to be more effective than imipramine.

Our methods of rating did not show any significant differences in the clinical results with the amine-oxidase inhibitors at the stated doses.

By contrast, the toxic effects were different. For a given degree of improvement in depression, pheniprazine produced the least derangement of liver function and iproniazid the most; nialamide occupied an intermediate position.

The work was financed by the St. George's Hospital medical research fund, and thanks are due to the chemical pathology department for facilities. We are grateful to Dr. Desmond Curran and the other consultants who referred cases to us from their clinics. Dr. W. J. Martin, of the department of medical statistics, University of London, kindly helped us with the statistical interpretation of the results.

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COMPARISON OF ANTIDEPRESSANT DRUGS IN DEPRESSIVE ILLNESSES

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A PAPER from this department (West and Dally 1959) on the effects of iproniazid in depressive syndromes emphasised its particular effectiveness in a group of "atypical depressions". In some of these cases, phobic anxiety symptoms predominated and sometimes obscured the underlying depression. Other patients complained mainly of exhaustion and fatigue, and might often show a picture of general inadequacy. Most of them were found, however, to have had capable, often rather driving, personalities before the onset of symptoms. Electroconvulsive therapy and other forms of treatment, including psychotherapy, had had little effect, and had sometimes made the patient feel worse.

Two types of response to iproniazid were obtained. In some patients the drug seemed to cure the illness, but in others the symptoms were only suppressed, and the drug had to be continued for long periods. Though reports of fatal hepatitis caused by iproniazid began to appear, we still felt justified in continuing to give the drug to those patients who were severely disabled by their symptoms and did not respond to treatment by other methods. There were only 6 (non-fatal) cases in over a thousand patients; but, as soon as new compounds—including analogues of iproniazid—appeared, a clinical trial seemed

essential to compare them with iproniazid, and to find out whether they were free from dangerous side-effects. Not enough serious work on this problem has yet been published in this country.

As soon as we felt we had learnt how to use the new drugs, we carried out controlled trials with several of them, to compare their efficacy with that of iproniazid and with one another. This paper reports our findings.

Method

Trials were first undertaken with 43 patients who were all known to respond well to iproniazid, but to relapse when that drug was stopped or when a placebo was substituted. Later, new patients were also referred from outpatient clinics after a diagnosis of depressive illness had been made. In all, 111 outpatients (69 cases of atypical, and 42 of endogenous, depression) took part in the trials.

Patients were used as their own controls. Each drug was given in turn for four weeks at a time:

Iproniazid, isocarboxazide (' Marplan '), and phenelzine (' Nardil ') were used to begin with; later, we included imipramine (' Tofranil '), nialamide (' Niamid '), and pheniprazine (' Cavodil '). The starting dose of each drug is shown in table I, line (a). Each drug was given in three equal doses throughout the day—the third not later than 7 P.M. in order to minimise possible sleep-disturbing effects. Patients were warned that they might feel dizzy when standing up suddenly or when bending over. They were asked to ignore this side-effect, if possible, as it would probably lessen or disappear after a few days. If there was no response after a fortnight, and provided side-effects were not too troublesome, doses were raised, as shown in table I, line (b). 1 elderly woman was unable to take more than 100 mg. a day of iproniazid. 3 patients experienced severe giddiness and ataxia when taking 150 mg. a day of imipramine, and had to reduce the dose to 75 mg. a day. When a patient had improved at the end of a four-week period, we gave a placebo for a further month. If he then remained well during this time we assumed that the illness had remitted, and we gave no credit to the last active drug. This happened in 23 cases. All drugs were then stopped and the patient was seen a month later. None relapsed during this time, though some did so in the next six months.

TABLE I—DOSE (MG.) OF DRUGS PER DAY

—	Iproniazid	Isocarboxazide	Phenelzine	Pheniprazine	Imipramine	Nialamide
(a)	150	30	45	18	150	150
(b)	150	40	60	24	225	225

(a) = initial dose. (b) = dose after 14 days.

Results

About 80% of patients who improved with iproniazid (grades 1 and 2 of table II) responded in some degree to isocarboxazide, phenelzine, and pheniprazine, but only about 50% did so with nialamide. But of those responding fully (grade 1) to iproniazid, only about 40% did as well with isocarboxazide, and phenelzine, and considerably fewer with nialamide and pheniprazine. These results are not in agreement with claims that these compounds are more potent inhibitors of monoamine oxidase than iproniazid and, by implication, are more effective clinically.

There were also differences in the reactions of individual patients to the different analogues of iproniazid. Although the total responses of the group to isocarboxazide, phenelzine, and pheniprazine were comparable, only about half the patients responded to each of these drugs in the same way (table III). A still greater difference existed between the response of a patient to these three drugs and to nialamide.

Imipramine is not a monoamine-oxidase inhibitor and differs from such drugs in its clinical effects. It is generally agreed that imipramine is more effective than iproniazid in the treatment of endogenous depression, but less effective in reactive forms of depression. Our results (table II) agreed with this . The 11 patients who responded fully to imipramine included 9 (82%) with endogenous depression. This contrasts with the 25 patients who did well with iproniazid, only 8 (32%) of whom had endogenous depressions. 2 of the patients who responded fully to iproniazid were among those responding equally well to imipramine.

TABLE II—COMPARISON OF IPRONIAZID WITH OTHER ANTIDEPRESSANTS

Response	Grade 1 (excellent)	Grade 2 (improved)	Grade 3 (no response)	Grade 4 (worse)	Total
Iproniazid	54*	6	2	0	62
Isocarboxazide ..	26	23	13	0	62
(Same patient in 23)					
Iproniazid	54*	7	5	0	66
Phenelzine	23	25	16	2	66
(Same patient in 21)					
Iproniazid	16*	2	0	0	18
Pheniprazine ..	4	10	0	4	18
(Same patient in 4)					
Iproniazid	25	10	10	4	49
Imipramine.. ..	11	13	14	11	49
(Same patient in 2)					
Iproniazid	27*	6	6	2	41
Nialamide	5	12	9	15	41
(Same patient in 2)					

* = $\chi^2 > 0{\cdot}01$

Side-effects

Side-effects tended to be proportional to the dose. They were commonest with iproniazid, and rarest with nialamide. Of the other monoamine-oxidase inhibitors, phenelzine seemed to cause more side-effects than isocarboxazide or pheniprazine. The following side-effects were seen: postural hypotension, especially in older patients; dizziness; paræsthesiæ; muscle twitching; dyspnœa; œdema; headache; blurred vision; dryness of mouth; delayed micturition; impotence; constipation; feeling of weakness; sweating; dermatitis; acne-like spots over upper half of body; and anæmia.

There were no cases of hepatitis. Transaminase estimations were done when the patient attended. There were transitory rises but no drug had to be stopped on this account. Outside this trial, however, 2 patients had jaundice one and two weeks after starting isocarboxazide and phenelzine respectively. Both had already been receiving iproniazid for some weeks before starting these drugs, and we thought the jaundice was due to the iproniazid. The need to watch for jaundice remains, particularly as a death during treatment with pheniprazine has been reported from the United States. It is

TABLE III—COMPARISON OF PHENELZINE WITH OTHER MONOAMINE OXIDASE INHIBITORS

Response	Grade 1 (excellent)	Grade 2 (improved)	Grade 3 (no response)	Grade 4 (worse)	Total	% showing same response
Phenelzine	22	20	16	2	60	
Isocarboxazide	21	25	13	1	60	53
(Same patient in 12)						
Phenelzine	5	12	8	2	27	
Pheniprazine	9	12	3	3	27	52
(Same patient in 1)						
Phenelzine	10	10	10	2	32	
Nialamide	4	6	8	14	32	22
(Same patient in 0)						

worth noting that we used iproniazid for eighteen months before we had a case of hepatitis, and then we had several in succession.

Discussion

Two criticisms may be made of the method we used. It is said that the effects of these drugs are not apparent for a month or more after starting treatment; and if this is true, our results would be vitiated. But we have found that if a drug is going to act in the particular type of patient tested, it will generally do so within a fortnight. Severe depressive states may take longer to respond, but these were not included in this trial as they usually require immediate electroconvulsive therapy.

These drugs are also said to have a carry-over effect that may mask the action of the succeeding compound. But generally when an antidepressant drug is stopped, provided the underlying depression is still present, symptoms begin to return within two weeks.

The results also confirmed our clinical impressions. None of the new analogues seemed as good as iproniazid, but in many cases isocarboxazide, phenelzine, and pheniprazine provided a satisfactory and, at the same time, safer form of treatment. All these drugs inhibit monoamine oxidase in vivo and in vitro. Some manufacturers claim that they exert " a truly selective action " on monoamine oxidase in the brain, and are much more potent in this respect than iproniazid. They imply that clinical effectiveness is directly related to monoamine-oxidase inhibition. Our results do not substantiate this view, and suggest that other enzymes and biochemical systems may also be involved. Some patients will respond only to iproniazid, and we feel justified in continuing to use it with care in patients who are severely disabled by their symptoms. Regular transaminase tests are done to give early warning of possible liver damage.

The mode of action of imipramine is still not known. It is more effective in endogenous than in atypical forms of depression, yet it overlaps clinically with iproniazid and its analogues, and there is no clear borderline between the two groups. There may be no basic distinction between these various types of depression—only degree of severity of symptoms. Interestingly, imipramine and iproniazid, or their analogues, will sometimes potentiate each other's effects.

A great deal more work, particularly in the biochemical field, remains to be done on depressive illness and on the actions of all the antidepressant drugs. Meanwhile a large group of selected patients can now be helped who were most difficult to treat before their introduction.

Summary

Iproniazid has been compared with imipramine, and with the monoamine-oxidase inhibitors (isocarboxazide, phenelzine, pheniprazine, and nialamide), in 111 outpatients, 79 of whom had " atypical " depressions.

Each drug was given in turn for four weeks, and the effects of each compared. 80% of patients who responded to iproniazid also improved in some degree with isocarboxazide, phenelzine, and pheniprazine; and about 50% did so with nialamide. But of patients responding fully to iproniazid, only 40% did as well with isocarboxazide and phenelzine, and considerably less than 40% with nialamide and pheniprazine.

Imipramine was more effective in endogenous than in atypical forms of depression, but there was a clinical overlap with iproniazid.

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PERFORATION OF THE URETHRA AND EXTRAVASATION OF URINE CAUSED BY A CALCULUS

Report of Two Cases

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PERFORATION of the urethra, and extravasation of urine in the absence of trauma, appears to be a most unusual complication of a urethral calculus. We have found only one other case in a child. Sukhavanam (1934) reported this condition in a boy, aged 6, whose signs and symptoms were almost identical with those of our patients. Jain (1935) described a patient, aged 35, in whom a large urethral calculus apparently " burst " spontaneously, and then caused extravasation of urine; Winsbury-White (1954) quotes two more cases in adults.

Two cases in children, seen within a few months at the Hacettepe Children's Hospital, Ankara, are therefore worth reporting. (The first case has been described previously by Eckstein et al. 1959.)

THE FIRST CASE

A boy, aged 8, was admitted on July 18, 1959. He was said to have been unwell for about 2 years, but he had shown no urinary symptoms until 3 days before his admission when he had become unable to pass urine, and complained of lower abdominal pain. There was no history of trauma to the pelvis or perineum, and no urethral instrumentation had been attempted.

He was pale, wasted, and dehydrated. He weighed 17 kg. (37 lb.), and had a pigeon-chest deformity and severe scoliosis. The anterior abdominal wall was œdematous as far as the umbilicus, and there was œdema in both flanks; the penis and scrotum were also œdematous, but there was no œdema below the inguinal ligament. The bladder was distended to about 5 finger breadths above the symphysis pubis, and was tense and tender when the boy was first seen. An hour later, however,

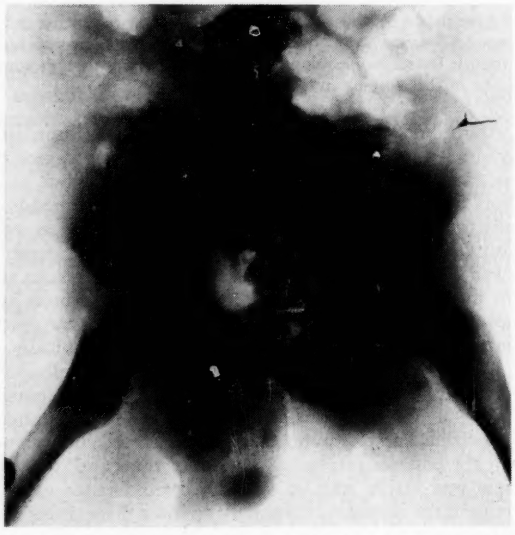

Fig. 1—Plain radiograph of abdomen showing soft-tissue œdema and bone deformities (case 1).

the bladder could no longer be felt, but the swelling within the abdominal wall had increased considerably, especially in the flanks. There was no external evidence of trauma to the perineum. Catheterisation was attempted, but a soft-rubber catheter was held up 5 cm. from the meatus.

The diagnosis of perforation or rupture of the urethra, possibly caused by a calculus, was made on clinical grounds.

No shadow suggestive of a radio-opaque stone, could be seen on a radiograph of the abdomen (fig. 1). There were many skeletal abnormalities including scoliosis, a deformed bony pelvis, and enlargement of the metaphyses with irregular calcification of the epiphyses. These changes are typical of severe rickets. There was soft-tissue swelling of the abdominal wall and scrotum, and the distended bladder could be seen.

Laboratory findings were: hæmoglobin 6·7 g. per 100 ml., non-protein-nitrogen (N.P.N.) 106 mg. per 100 ml., blood-CO_2-combining-power 10·5 mEq. per litre, and blood-chlorides 106 mEq.

Operation

After a preliminary blood-transfusion, the abdomen was opened by a vertical incision below the umbilicus. The bladder was found to be thick-walled and distended, and contained 500 ml. of clear urine (which later proved to be sterile on culture). The bladder-neck was wide open, and a finger could easily be passed into the prostatic urethra. At this stage a metal sound was carefully introduced into the urethra. The sound passed easily into the bladder, meeting no obstruction. Inspection of the ureteric orifices showed urine coming freely from the left orifice, but none came from that on the right. Because of the boy's poor condition, further exploration to find the cause of extravasation was considered unjustifiable, and the bladder was closed around a large Pezzer catheter. Separate drains were left in the prevesical tissues and in the abdominal wall.

The patient's immediate postoperative condition was satisfactory; the urine output was good, the scrotal swelling disappeared within 3 hours and the œdema of the abdominal wall within 16. On the 2nd day the boy's condition deteriorated, and, although he had a urine output of 1200 ml. in 48 hours, his N.P.N. rose to 130 mg. per 100 ml. His temperature was then 40°C (104°F). He became drowsy, and finally comatose. In spite of intensive antibiotic therapy, he died on July 25, 6 days after admission. A blood-culture yielded a growth of *Escherichia coli*.

Fig. 2—Plain radiograph of abdomen showing tissue œdema and two small urethral calculi (case 2).

Necropsy

The bony changes were confirmed. There was consolidation of the upper lobe of the right lung. The liver showed fatty degeneration. The left kidney was enlarged and moderately hydronephrotic, and the left ureter was slightly dilated. There was a soft calculus 2 cm. above the left vesicoureteric junction. The right kidney was small and fibrotic; the ureter normal. The bladder was hypertrophied. The urethra was widely dilated, and, at the penoscrotal junction, there was a rent in its dorsal surface leading to a small cavity which contained a stone, 1 cm. in diameter.

The stone, on chemical analysis, was found to contain uric acid only. The cause of death was considered to be *Esch. coli* septicæmia.

THE SECOND CASE

A boy, aged 2, was admitted on Nov. 15, 1959, with a history of passing urine drop by drop for 15 days. For 3 days he had passed no urine at all. During this time his abdomen, scrotum, and penis had become swollen. There had been no trauma to the pelvis or perineum, and no urethral instrumentation had been attempted. He was wasted and very ill, weighing only 8·7 kg. (19 lb.). His temperature was 37°C (98·6°F). The abdominal wall was œdematous to the umbilicus, and the scrotum and penis were grossly swollen. There was a fluctuant swelling in the perineum, and the bladder was distended to 5 finger breadths above the symphysis pubis. There was no œdema below the inguinal ligament, and the distribution of the tissue swelling was typical of extravasation of urine.

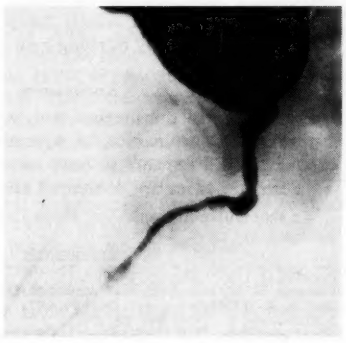

Fig. 3—Micturating cystourethrogram showing normal urethra (case 2).

A plain radiograph of the abdomen confirmed the presence of soft-tissue œdema (fig. 2). In the midline, below the pubic symphysis, two small irregular shadows were seen, which could have been those of small urethral stones.

Hæmoglobin was 6·4 g. per 100 ml., N.P.N. 114 mg. per 100 ml., calcium 7·5 mg., phosphorus 3·7 mg., and alkaline phosphatase 5·3 King-Armstrong units.

Operation

The bladder was opened through a short vertical midline incision, and was found to contain some 800 ml. of turbid urine (which on culture yielded *Esch. coli*). A metal dilator could easily be passed through the urethra and no obstruction was met. The bladder was closed around a large Pezzer catheter, and the prevesical tissues and abdominal wall were drained. The perineum was then opened and urine escaped freely from the tissues. Two small sharp stones were found lying loose in the perineal tissues; the urethra could not be identified. The perineal wound was closed with drainage.

After a stormy convalescence, he had a tension pneumothorax on Nov. 25, which was treated with an intercostal drain. Pus from the pleural cavity yielded *Pseudomonas pyocyanea*. The suprapubic tube was accidentally pulled out one month after its original insertion, but, as attempted catheterisation showed that a soft-rubber catheter passed subcutaneously into the anterior abdominal wall and not into the bladder, a perineal urethrostomy was established.

An excretion urogram on Dec. 17 showed normal kidneys and ureters. His general condition improved slowly, and the perineal catheter was removed on Jan. 20, 1960. The boy passed urine with a good steam almost immediately. A micturating cystourethrogram, taken a week later, showed no

reflux into the ureters, and the urethra appeared completely normal (fig. 3). The boy was discharged on Feb. 12, weighing 10 kg. (22 lb.).

Discussion

The two cases described, as well as the one reported by Sukhavanam (1934), showed the same clinical picture on admission. Both our patients were severely undernourished —a point of interest, since severe malnutrition appears to be uncommon in our other patients with urolithiasis. There is no doubt that both children had extravasation of urine; the distribution of the œdema and the absence of redness or tenderness would exclude a cellulitis. Presumably, the stones ulcerated the urethral mucosa which then became œdematous and closed off the urethral lumen so that urine was forced into the tissues on attempted micturition.

Diversion of the urine either through a suprapubic cystostomy or by a perineal urethrostomy is essential; in the presence of much perineal œdema, a cystostomy is the easier operation. Case 2 shows that a badly damaged urethra is able to heal without the formation of a stricture even when no primary suture has been attempted. A strip of urethra had probably remained in continuity, allowing a new tubular structure to form—a process comparable with that which takes place when a hypospadias is repaired by burying a strip of urethra (Browne 1953).

Summary

Perforation of the urethra and extravasation of urine is a very rare complication of a urethral stone. Only one case in a child appears to have been reported previously. Two further cases are presented and discussed.

We should like to thank Prof. Ihsan Dogramaci for permission to publish these cases.

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MUSCULAR SARCOIDOSIS

A Case with "Tumour" Formation

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MUSCULAR lesions are common in sarcoidosis, but do not usually produce symptoms and signs of muscular involvement. "Sarcoid tumours" of the skeletal muscles are even rarer. In our patient two organs usually spared—the stomach and the pancreas—were also affected. Sarcoid granulomas were also found on a nerve-bundle.

Case-report

A 55-year-old Negress had a bilateral ligation for varicose veins in the legs in 1956. Three months later, two small nodules appeared above the incisions. During the next six months she noted similar swellings in the lumbar region and right arm. The arm nodules arose at the site of an unimportant trauma. Two years before admission, increasing weakness and numbness of the legs had begun. By May, 1958, she could not move the left leg. Self-treatment with hot applications resulted in a third-degree burn. On Dec. 18, 1958, she was admitted to the John Sealy Hospital. The past history was irrelevant except for "measles" at 26, after which she had generalised seizures about once a month. Her mother died of "tuberculosis" several years ago.

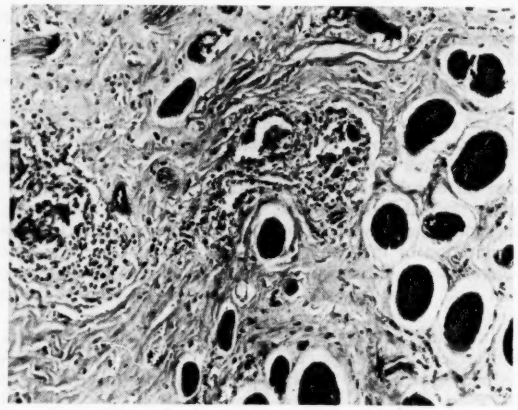

Fig. 1—Infiltration and separation of striated-muscle fibres (dark areas) by sarcoid lesions. Phosphotungstic acid-hæmatoxylin, × 100.

She appeared chronically ill. The speech was slurred. The eyes, lungs, and heart were normal. The liver and spleen were not palpable. In each inguinal area there was a hard mass $8 \times 10 \times 4$ cm. On the extensor surface of the right forearm there was a round mass 5 cm. in diameter. Similar masses were seen on both thighs. These masses, which were not tender, were unattached to the skin and appeared to move with contraction of the underlying muscles. The lumbar muscles were hard and about twice the normal size. The inguinal lymph-nodes were moderately enlarged. There were bilateral varicosities in the legs, and a healing third-degree burn over the left tibia. There was hypæsthesia below the level of L2. Flaccid paraplegia was almost complete. Vibratory and position senses were absent in the lower limbs.

Urinalysis was negative. Hæmoglobin 11·8 g. per 100 ml., leucocytes 11,300 per c.mm. (47% eosinophils). This eosinophilia did not vary up to the time of death. Total serum-protein was 7·1 (albumin 3·1 and globulin 4·0) g. per 100 ml. Serum electrophoresis showed slight heterogeneous increase in the gamma-globulin fraction. Serum levels of sodium, potassium, chloride, CO_2-combining power, calcium, phosphorus, alkaline-phosphatase, creatine, and bilirubin and blood-urea nitrogen were all normal. Fasting blood-sugar was 60 mg. per 100 ml., sedimentation-rate 35 mm. in first hour (Wintrobe), thymol turbidity 9·5 units, cephalin flocculation ++, prothrombin-time 40% of normal. Stools were negative for ova and parasites. Urinary excretion of vitamin B_{12} was 20% in twenty-four hours (Schilling's method); twenty-four-hour urinary creatine excretion 277 mg. The cerebrospinal fluid was repeatedly normal. An electrocardiogram was negative; an electroencephalogram revealed evidence of convulsive disorder.

A chest radiograph showed questionable mediastinal widening. X-rays of the gastrointestinal tract and bone were normal. An intravenous pyelogram revealed a small radio-opaque calculus in the right renal pelvis.

A biopsy from the right inguinal mass showed chronic granulomatous reaction (fig. 1) involving the subcutaneous tissue and striated muscle. Special staining did not show fungi or acid-fast bacilli. Biopsy specimens from the mass in the right arm, and from the right gastrocnemius muscle (seemingly uninvolved) revealed identical pictures, though the left gastrocnemius showed non-specific chronic inflammatory changes with focal areas of atrophy. A liver biopsy was normal. A neurologist (Dr. Walter Klingman) agreed with the diagnosis of peripheral neuropathy. Four weeks after admission, prednisone 5 mg. four times daily, vitamin-B complex, and physiotherapy were begun. By the second week of therapy,

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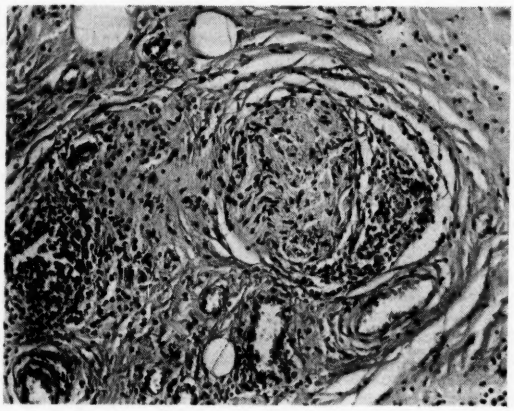

Fig. 2—Infiltration of epineural sheath of nerve-bundle (middle figure) by sarcoid lesion. Hæmatoxylin and eosin, ×100.

she was able to walk with crutches. Two months after admission, while receiving physiotherapy, she suddenly had a generalised seizure, became cyanotic, and died within a few minutes.

Necropsy

Death had resulted from occlusion of the main branches of the pulmonary artery by a large embolus. There were masses in the inguinal regions, arm, and thighs. Similar bilateral paravertebral masses were found in the lower lumbar region. Cut surfaces of these masses revealed grey-pink firm tissue embedded in, and protruding from, the muscle-bundles. Mediastinal lymph-nodes were much enlarged. Numerous small nodules, particularly in the perihilar regions, were present in both lungs. The stomach contained a discrete mass, 2 cm. in diameter, in the posterior wall near the pylorus. It was raised a few millimetres above the mucosal surface. Within the head of the pancreas, there was a sharply demarcated nodule 1·5 cm. in diameter. The spleen contained numerous scattered nodules. The liver appeared normal. A small calculus was found in the right renal pelvis. Nothing else abnormal was found.

Histological Findings

Sections from the lungs, spleen, cervix, muscular masses, and lymph-nodes showed lesions typical of sarcoidosis. Acid-fast bacilli and fungi were not found with special staining. The gastric and pancreatic nodules were similar, with numerous eosinophils. Section of a small nerve-bundle in the paralumbar muscle showed a sarcoid granuloma infiltrating the epineural sheaths (fig. 2).

Discussion

Sarcoid tubercles in the skeletal muscles were reported early in this century (Licharew 1908, Bloch 1914); and this was regarded as a rare finding, until Myers et al. (1952) studied random muscle biopsies. Muscles may be involved in as many as 50% of cases of sarcoidosis (Wallace et al. 1958a and b), which is comparable with the incidence of pulmonary involvement (Longcope and Frieman 1952). In most patients, muscular sarcoidosis remains clinically inapparent. In rare cases, muscular symptoms predominate.

Although sarcoid myopathy has no well-defined clinical features, Lafon et al. (1955), for convenience, divided symptomatic muscular sarcoidosis into the atrophic and tumour forms. Both may occur in the same patient (Muchka and Orzechowski 1919). Exceptionally, generalised muscular hypertrophy has been reported (Furtado and Carvalho 1947).

Atrophic muscular sarcoidosis is relatively more common than the other forms. Atrophy may be slight (Powell 1953), isolated (Powell 1953, Lafon et al. 1955, Coërs 1956, Coërs et al. 1956) or diffuse (Bates and Walsh 1948). More often proximal muscles of the limbs are involved (Ammitzboll 1956, Harvey 1959). It has simulated myasthenia gravis with a slightly positive neostigmine response (Devic et al. 1955), dermatomyositis (Weinberger 1933), progressive muscular dystrophy (Muchka and Orzechowski 1919, Bates and Walsh 1948, Powell 1953), and amyotrophic lateral sclerosis (deMorsier et al. 1954). In advanced cases, muscular contractures develop (Warburg 1955), or muscles transform into fibrous cords (Snorrason 1947, deMorsier at al. 1954). Still's disease may be mimicked when there is associated joint disease (Castellanos and Galan 1946).

The " sarcoid tumours " of the skeletal muscles are rare. We have been able to collect only 13 cases from the literature (Bergel and Scharff 1933, Sundelin 1935, Pautrier 1939, Harrell 1940, Bates and Walsh 1948, Krabbe 1949, Powell 1953, Klotz et al. 1955, Lafon et al. 1955). The distribution of the " tumours " is irregular. Isolated nodules have been found anywhere—even on the skull (Lafon et al. 1955). Although they may be diffuse, they are more often localised on the extremities. They resemble " subcutaneous nodules " on palpation (Powell 1953). Klotz et al. (1955) found them at the musculotendinous junction. Usually they are situated in the muscle mass itself, unattached to the overlying skin, and move during muscle contraction. The size of the " tumours " has been reported to change from a few millimetres to the size of a hen's egg (Sundelin 1935). They are firm or hard and seldom tender. Apart from the nodules, the patients may be symptom-free (Sundelin 1935), or may complain of generalised weakness (Harrell 1940). The present patient was paraplegic. In addition to muscular involvement, she had peripheral neuropathy. In sarcoid myopathy, disability seems to depend more upon atrophy of the muscles than upon the " tumour " itself and, particularly, is determined by nervous-system involvement. Peripheral neuropathy in sarcoidosis is common (Colover 1948, Martin 1955). In our patient, a sarcoid tubercle was found on a nerve bundle—a most unusual site.

The histological picture of muscular sarcoidosis has been extensively reviewed (Adams et al. 1953, Devic at al. 1955, Martin 1955, Maurice 1955, Myers et al. 1952, Powell 1953, Wallace et al. 1958a and b, Walton and Adams, 1958). Essential features include sarcoid tubercles, interstitial inflammation with fibrosis, and disruption and atrophy of the muscle fibres. These findings probably explain the increased creatinuria in some patients (Powell 1953).

Symptomatic or asymptomatic muscular sarcoidosis seems to be part of the systemic disease. Although isolated muscular sarcoidosis has been reported, this interpretation seems improbable. There was no necropsy confirmation in these cases. In our patient, necropsy showed that the disease was diffuse. Sarcoid granulomas, undetected during life, were discovered in the stomach and pancreas. Sarcoidosis of the stomach (Schaumann 1936, Kulka 1950, McKusick 1953, Pearce and Ehrlich 1955) and pancreas (Cotter 1939, Nickerson 1937, Ricker and Clark 1949) are rare; both are reported as parts of the generalised disease.

Summary

Unusual features in a patient with sarcoidosis were involvement of the skeletal muscles and the formation of large nodules in the stomach, pancreas, and a nerve-bundle. Asymptomatic muscular sarcoidosis is common but predominant involvement of the striated muscle with related disability is rare.

Muscular sarcoidosis does not seem to be a well-defined clinical entity, but rather simulates other muscular diseases. In sarcoid myopathy, disability depends more upon atrophy and nervous-system involvement than upon the presence of sarcoid " tumours ".

References overleaf

ACCIDENTAL PNEUMATIC RUPTURE OF ŒSOPHAGUS AND STOMACH

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PNEUMATIC rupture of colon or rectum, resulting from the release of compressed air near the anus, has often been reported. Similar rupture at the opposite end of the alimentary canal seems less common.

Petren (1909) reported rupture of the œsophagus in a 27-year-old man who, in a gesture of mirth, applied a compressed-air hose to his mouth. At necropsy, a 6 cm. rent was found in the left posterolateral wall of the lower œsophagus. Borghero (1953) reported a ruptured œsophagus from compressed methane gas. A most curious episode was reported by Kerr et al. (1953). A 3-year-old boy bit through the inner tube of a tractor tyre which was herniating through a defect in the outer cover. The rush of compressed air caused a linear tear in his lower œsophagus, and produced a pneumothorax. After rib resection and drainage, he recovered. Hood (1957) described a young man whose lower pharynx and upper œsophagus were torn when a carbon-dioxide fire extinguisher exploded in his face. He was successfully treated by drainage of his neck, a tracheostomy, and feeding through a gastrostomy.

Pneumatic rupture of the stomach seems even less common, and most cases are associated with the administration of nasal oxygen by catheter. Fenton (1956) described a fatal stomach perforation in an adult when a nasal oxygen catheter, inserted by the anæsthetist post-operatively, slipped past the cricopharyngeus, and slowly blew up the stomach. Gain (1958) reported a similar case. In newborn children, oxygen administration by an oropharyngeal catheter is common practice. Pendergrass and Booth (1946) and Musser (1956) report examples of stomach rupture after this procedure. The so-called idiopathic perforation of the stomach in the newborn has occurred without oxygen administration (Vargas et al. 1955, Castleton and Hatch 1958, Hamrick 1959).

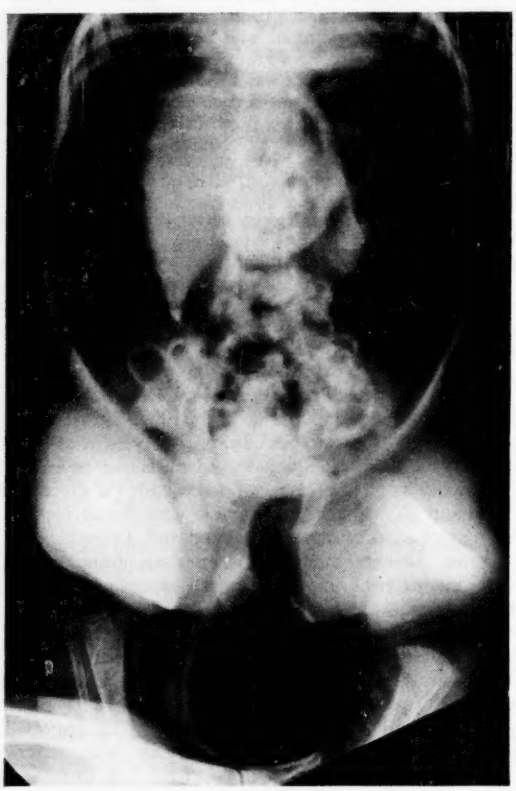
We describe here two cases of pneumatic rupture of the foregut, one involving the œsophagus, and the other the stomach. This second case has been briefly recorded elsewhere (Spencer 1958).

Case-reports

Rupture of the Œsophagus

A healthy engineer, aged 39, was unloading some small fire extinguishers from a truck, when the valve of one suddenly discharged close to his face while he was talking. He felt an immediate pain across his lower chest, but, apart from being momentarily dazed, he was not otherwise injured. Within the next two hours, a deep-seated severe retrosternal pain developed and he became progressively more breathless, preferring to lie with the left side of his chest dependent. He had difficulty in swallowing saliva.

On admission, he was moderately shocked and clearly in great pain. There was slight surgical emphysema of the neck, some bruising of the pharynx, and the abdomen was rigid without being unduly tender. Auscultation of the left chest below the nipple revealed a curious sound which suggested a to-and-fro slapping of fluid and air. A chest radiograph showed a shallow left pneumothorax and a widened mediastinal shadow with considerable mediastinal emphysema. A 'Neo-Hydriol' swallow showed that the lower œsophagus was displaced to the right, with most of the contrast medium lying outside the lumen, just above the diaphragm. No contrast medium had entered the stomach or pleural space.



Radiograph before operation, showing abdominal distension and patent processus vaginalis.

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A diagnosis of pneumatic rupture of the lower œsophagus was made; and a left thoracotomy, through the bed of the 7th rib, was performed six hours after the accident. There was a little clear fluid and air in the pleural space, but the lung was undamaged. The lower posterior mediastinum was bulging and emphysematous; and, when incised, oily contrast medium was seen to be lying in an extensive para-œsophageal space. The œsophagus had a 9 cm. vertical rent, extending upwards from immediately above the diaphragm. No further tear could be felt by a finger inserted past the pouting mucosa into the lumen, and the cardia was normal. The rent was readily sewn up with a continuous atraumatic catgut suture, reinforced with further interrupted stitches. A nasogastric tube was passed. The chest was closed with drainage; but, next day, a loculus of pus required further drainage. He had a diffuse suppurative bronchitis, confirmed by bronchoscopy. Feeding by gastric tube was continued for five days, and he was given fluids only until the tenth day. When he left hospital on the eighteenth day, he was taking soft foods. Barium swallow a month later showed a normal œsophagus, and his subsequent progress has been satisfactory.

Rupture of the Stomach

A newborn full-term male infant was rather limp after a natural delivery. Though breathing was established there was an excess of pharyngeal mucus which had to be sucked out. Oxygen was given through an intraoral catheter at 2 litres per minute, the baby's mouth being held closed. Almost immediately, to the nurse's amazement, the baby's scrotum began to inflate like a balloon. The oral catheter was hurriedly withdrawn. The abdomen was drum-tight, and a radiograph left no doubt about the diagnosis of pneumoperitoneum, probably from a rupture of the stomach (see figure). The baby's condition remained surprisingly good.

At laparotomy, five hours after birth, peritoneal incision produced an audible pop with escape of gas. A rupture 1 cm. long was found on the posterior aspect of the greater curvature of the stomach, directly opposite the œsophagogastric junction. Closure was readily done with atraumatic catgut. Fourteen hours after operation, the child swallowed electrolyte solution satisfactorily. Next day milk feeding was begun and continued without upset. Mother and baby were discharged from the maternity ward after the average primipara's stay of twelve days.

Discussion

We believe these two unusual cases throw some light on the mechanism of rupture of the foregut; and, in particular, on the level of rupture.

When there is a sudden rapid rise in pressure in the mouth, as in the engineer, the pressure is transmitted to the laryngopharynx and enters the respiratory passages causing a reflex closure of the glottis. The air then forces the cricopharyngeal sphincter to give way and produces sudden distension of the œsophagus. The cardia fails to relax, as it does in the slower-coordinated reflex of swallowing, and the dilated œsophagus ruptures. If, however, the pressure is allowed to build up more slowly, as in the baby, both the cricopharyngeus and the cardiac-sphincter mechanism relax, and the stomach bears the brunt of the distension and eventually ruptures. In the case described by Hood, the cricopharyngeus held tight for a longer period and the pharynx also ruptured.

When, on the other hand, there is a sudden rise of pressure at the lower end of the foregut, as in the incoordinate vomiting associated with spontaneous rupture of the œsophagus and also in abdominal crush injuries (Aldrich and Anspach 1939, Nelson 1959), it is the cardia which gives way and the cricopharyngeus which fails to relax as it does in the more coordinated act of vomiting. Once again, the œsophagus distends and ruptures.

In both situations, the interesting feature is that it is the lower left wall of the œsophagus which usually ruptures. A number of writers on the subject of " spontaneous " rupture of the œsophagus (Mackenzie 1884, Mackler 1952, Bodi et al. 1954) have performed experiments on the fresh postmortem œsophagus. They found that a pressure of 5–10 lb. per square inch was required, and that rupture was almost always in the lower left wall. It seems clear that the œsophagus here is either weaker or, more probably, less well supported by surrounding structures. Reflux œsophagitis may sometimes be a causal factor.

Since intragastric oxygen has been recommended as a resuscitative measure, it is surprising that the accident that happened to the baby has not been more frequent. The correct practice when oxygen is given by oral or nasal catheter is to use a second catheter as a safety valve. The presence of a patent processus vaginalis undoubtedly saved this baby from a fate comparable with that of the Michelin man, and also led to an early diagnosis and closure of the perforation before the peritoneum was seriously soiled. It is reasonably certain that this rupture was not produced by the catheter itself which was introduced for only a few centimetres. Probably, when the mouth was held tightly shut, the nasal airway was also obstructed, causing œsophageal and gastric distension and eventual rupture of the stomach.

Another feature in the first case was the diffuse tracheobronchitis, which was a lesion probably comparable with the blast injury described during the late war.

Summary

Two examples of pneumatic rupture of the foregut suggest that the site of rupture depends on the speed at which pressure builds up.

The administration of oxygen by oral or nasal catheter to newborn infants can rupture the stomach.

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". . . among the dynamic properties of the nervous system, there are some very important ones that have been largely neglected and . . . our ignorance of these bars the way of advance in neuropathology and in our understanding of the genesis and nature of nervous diseases. Take, for example, such questions as that of the blood-brain barrier and of the extracellular spaces in the brain. . . . Clinical training, with a smattering of morbid anatomy, clinical pathology, empirical electroencephalography, and textbook psychiatry, no longer is a truly scientific training for research into basic problems of nervous disease. . . . I believe that we must look to the training of a new kind of experimental neuropathologist who, collaborating, as Payling Wright suggests, with physiologists, embryologists, biochemists, and immunologists, can first tackle the basic research in physiology that has so far been neglected and from that seek to build a scientific knowledge of the etiology and nature of disease processes."—Sir FRANCIS WALSHE, *World Neurology*, 1960, **1**, 189.

Preliminary Communications

SEPARATION AND ESTIMATION OF ADRENAL STEROIDS IN THE URINE OF NEWBORN INFANTS

IN the first few days of life the adrenal gland of the human infant undergoes dramatic structural changes. The fœtal zone, which constitutes the major part of the gland at birth, involutes whilst the histologically different adult type of cortex gradually develops. These changes occur at the critical time of adaptation to an extra-uterine existence, and the method presented for the separation and estimation of urinary steroids has been devised for study of adrenal function during this period.

When any of the usual group methods for steroid assay are applied to the urine of infants the specificity of the results is very doubtful, mainly because of the relative preponderance of non-steroid chromogen which is estimated together with the steroid material in the crude extract. To obtain relatively pure extracts it is necessary to modify these methods, and this involves procedures which are little less complex than those required for separation of individual steroids. Group determinations have therefore been abandoned in favour of the estimation of individual compounds, which gives more valuable information.

METHOD

Assays are carried out on one-tenth of 24-hour specimens of adult urine and on 100 ml. of pooled 24-hour specimens obtained from newborn infants in the first 3 days of life. Inevitable losses, due to the lengthy procedure, are assessed by means of isotope recovery.

Little information is available on the nature of the steroid conjugates present in the urine of newborn infants, but a preliminary investigation has shown that the maximal yield of free steroids is obtained only when two separate enzyme preparations are used with two separate hydrolyses and extractions. The amount of steroid material which is obtained thereafter by continuous ether extraction of the hydrolysate at pH 0·8 is not significant.[1]

Enzyme inhibitors are removed by barium-chloride precipitation.[2] The urine pH is then adjusted to 4·8, streptomycin and penicillin are added, and the first hydrolysis is carried out at 40°C for 20 hours using the succus entericus of the snail *Helix pomatia*. The resulting free steroids are extracted by an ether/ethyl-acetate mixture (2/1 by vol.), the extract then being washed with *N*NaOH followed by water to which has been added a few drops of glacial acetic acid.[3] The hydrolysis is repeated on the aqueous phase using an enzyme preparation from the visceral hump of the limpet *Patella vulgata*.[4] The extraction is repeated as before and the washed extracts are combined and evaporated to dryness at a temperature below 40°C.

The Bush system of chromatography (Bush B_3 system, light-petroleum/benzene/methanol/water 66/33/80/20 by vol., Whatman 3 MM paper) is used to separate the steroids into three fractions of different polarity.[3] Fraction I contains mainly 17-oxosteroids, fraction II the 11-oxy-17-oxosteroids, and fraction III the more polar C_{21} corticoids. Fractions I and II are eluted and applied directly to the final chromatograms. The eluant of fraction III requires further purification.

It is partitioned between an ether/ethanol mixture and water containing ammonium sulphate.[5] The organic phase is evaporated and further impurities are frozen out at −20°C from an ethanolic solution. The extract is applied to Whatman 3 MM paper and reverse-phase chromatography in heptanol/water (1/9 by vol.) is carried out at 21°C.[6] In this system, the highly polar C_{21} steroids run off the paper and are collected for 20 hours while the impurities remain on the paper. The C_{21} steroids are extracted from the overflow with ether/ethyl-acetate (2/1 by vol.) and the extract is evaporated to dryness.

The final chromatographic and steroid detection methods used are slight modifications of those described by Bush and Mahesh:[7]

Suitable proportions of each fraction are applied in ethanol to strips of Whatman 42 paper. Fraction I is developed for 6·5 hours in a modified Bush A system, light-petroleum/methanol/water (100/85/15 by vol.) at 21°C and fraction II is developed for 11 hours in the Bush B_3 system at 26°C. Appropriate quantities of fraction III are placed on two groups of papers which are developed in a modified Bush B4 system, toluene/methanol/water (4/3/1 by vol.). One group is developed for 20 hours for resolution of the tetrahydro and more polar compounds, and the other for 6 hours for resolution of the remaining C_{21} steroids—cortisol, cortisone, dihydrocortisone, and corticosterone.

The majority of the steroids in fractions I and II are estimated by scanning the papers after treatment with Zimmermann reagent, using a suitable photoelectric scanner, the scans being compared with those of standard papers. A blue tetrazolium reagent is used in a similar manner to evaluate the reducing steroids present in fraction III. Δ^4-3-oxosteroids in fraction III are detected and measured by their fluorescence after treatment with a sodium hydroxide reagent. At present the identification of steroids is based entirely on the Rf values found in the chromatographic systems used. Physical and chemical methods are being employed to establish final identification.

At least one 4-^{14}C-steroid in each fraction is added to the urine sample at the beginning of the assay, and final determination of radioactivity is made by elution from the chromatograms and end window counting. Any losses found are applied as a correction to the other steroids assayed in the fraction. Recoveries for all steroids in fractions I and II are based on that of radioactive Δ^4-androstenedione and androstenetrione respectively. Either two or three labelled steroids are used to assess recovery in fraction III. The most polar compound available is tetrahydrocortisol, the recovery of which must be used to correct for any losses of the more polar 6-hydroxy compounds. Theoretically the 6-hydroxy compound values corrected in this way may be less than the actual 24-hour output.

RESULTS

Although principally designed for infant urine, the method has been applied to adult urine to allow comparison with other methods. The results obtained for adult males and females fall within the ranges quoted by other writers.[7–11] Many steroids are assayed on each chromatogram, and for various technical reasons the accuracy of the result varies from compound to compound. Results showing poor replication have been included for comparative purposes but are specially marked in the table. Conclusions have been drawn only from results showing good replication, and differences have been considered valid only if they have been proved statistically by the application of the " t test " for significance.

The table gives values for pooled 24-hour specimens of urine from five normal adult males, six normal adult females, five mothers for the 24-hour period immediately following normal delivery, sixteen full-term male infants aged 1–3 days, and five premature male infants aged 1–3 days.

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URINARY STEROID OUTPUT IN MICROGRAMMES PER 24 HOURS
(The numbers of replicate estimations are given in parentheses.)

Steroid	Normal male	Normal female	Maternal post-delivery	Normal infant	Premature infant
Fraction I:					
Dehydroepiandrosterone	1500 (*8*)	1500 (*12*)	490 (*9*)	0 (*5*)	4 (*1*)
Ætiocholanolone	2100 (*6*)	1700 (*12*)	860 (*11*)	0 (*5*)	0 (*2*)
Androsterone	1800 (*7*)	1600 (*13*)	1400 (*10*)	0 (*5*)	0·9 (*1*)
Fraction II:					
11β-Hydroxyætiocholanolone	880 (*3*)	470 (*7*)	190 (*7*)	12 (*4*)	9·9 (*2*)
11β-Hydroxyandrosterone	1000 (*3*)†	740 (*6*)†	360 (*6*)†	29 (*4*)†	9 (*2*)†
11-Oxoætiocholanolone	1100 (*4*)	780 (*7*)	580 (*9*)	20 (*5*)	33 (*3*)
11-Oxoandrosterone	340 (*4*)	220 (*4*)	210 (*6*)	12 (*4*)	0 (*3*)
Fraction III:					
6-Hydroxy and more polar compounds*	260 (*2*)	210 (*6*)	1300 (*7*)	52 (*5*)	25 (*2*)†
Total tetrahydro compounds	6100 (*4*)	5100 (*10*)	9800 (*12*)	450 (*10*)	470 (*2*)
Tetrahydrocortisol	2200 (*3*)	1800 (*9*)	4400 (*12*)	180 (*13*)	150 (*2*)
allo Tetrahydrocortisol	540 (*1*)	840 (*7*)	1600 (*5*)	. .	120 (*1*)
Tetrahydrocortisone	3300 (*3*)	2500 (*10*)	4800 (*12*)	240 (*11*)	260 (*2*)
Cortisol*	320 (*2*)	100 (*6*)	1000 (*7*)	25 (*5*)	6·2 (*2*)
Cortisone*	210 (*2*)	130 (*5*)	470 (*5*)	12 (*6*)	6·9 (*2*)
Dihydrocortisone	480 (*2*)	840 (*3*)	2000 (*11*)	110 (*9*)†	260 (*1*)
Corticosterone*	220 (*1*)	68 (*5*)	500 (*6*)	44 (*5*)	31 (*2*)

* Compounds estimated by their sodium fluorescence. † Results showing poor replication.

The following trivial names have been used in the above table and in the text:

Dehydroepiandrosterone	3β-Hydroxyandrost-5-ene-17-one
Ætiocholanolone	3α-Hydroxy-5β-androstan-17-one
Androsterone	3α-Hydroxy-5α-androstan-17-one
11β-Hydroxyætiocholanolone	3α:11β-Dihydroxy-5β-androstan-17-one
11β-Hydroxyandrosterone	3α:11β-Dihydroxy-5α-androstan-17-one
11-Oxoætiocholanolone	3α-Hydroxy-5β-androstan-11:17-dione
11-Oxoandrosterone	3α-Hydroxy-5α-androstan-11:17-dione
Tetrahydrocortisol	3α:11β:17α:21-Tetrahydroxy-5β-pregnan-20-one
Tetrahydrocortisone	3α:17α:21-Trihydroxy-5β-pregnan-11:20-dione
allo Tetrahydrocortisol	3α:11β:17α:21-Tetrahydroxy-5α-pregnan-20-one
Cortisol	11β:17α:21-Trihydroxypregn-4-ene-3:20-dione
Cortisone	17α:21-Dihydroxypregn-4-ene-3:11:20-trione
Corticosterone	11β:21-Dihydroxypregn-4-ene-3:20-dione
Dihydrocortisone	17α:21-Dihydroxy-5β-pregnan-3:11:20-trione
Δ^4-Androstenedione	Androst-4-ene-3:17-dione
Androstenetrione	Androst-4-ene-3:11:17-trione

Fraction-I steroids are relatively unimportant constituents of the urine of newborn male infants.

Small quantities of dehydroepiandrosterone have been found in the pooled urine of premature babies but not in the pooled urine of full-term babies, although trace amounts of this steroid have occasionally been detected in the urine of full-term babies studied individually. Ætiocholanolone has not been detected in the pooled urine of premature or full-term infants. Androsterone has been found in the pooled urine of premature infants in trace amounts but not in the pooled urine of full-term infants. Again trace amounts of androsterone have been obtained from some full-term babies studied individually.

The output of dehydroepiandrosterone and ætiocholanolone is lower in maternal than in non-pregnant female urine. Androsterone levels are the same in the two groups. A greater number of unknown compounds, less polar than androsterone, and staining with Zimmermann reagent, have been detected in premature-infant and full-term-infant urine and in maternal urine than in adult male and female urine.

The fraction-II steroids, 11β-hydroxyætiocholanolone, 11β-hydroxyandrosterone, and 11-oxoætiocholanolone, have been found in the urine of premature and full-term infants. 11-Oxoandrosterone is present in pooled urine from full-term infants, and, although absent from the pooled urine of premature infants, it has been detected in very small quantity in the urine of a premature infant studied individually.

A significant Zimmermann-staining band with an Rf value corresponding to that of 11β-hydroxyandrost-4-ene-3:17-dione has been found consistently in maternal, full-term-infant, and premature-infant urine. Sodium fluorescence and blue tetrazolium staining are also shown in the same area but to a lesser degree, and it is assumed that more than one compound is present. The dominance of Zimmermann staining over fluorescence implies that 11β-hydroxyandrost-4-ene-3:17-dione is not the principal compound involved. A band with an Rf value similar to that of androstenetrione and staining deeply with blue tetrazolium has been found consistently in maternal and infant urine.

The excretion of C_{21} steroids appears to be similar in full-term and premature infants. In the pooled urine of infants corticosterone is present in greater quantity than cortisol. The output of total 6-hydroxy compounds, total tetrahydro compounds, cortisol, cortisone, and corticosterone is greater in maternal urine in the 24 hours following delivery than it is in adult female urine.

CONCLUSIONS

Although the results given here are obtained from pooled urine, the method has been devised for the estimation of the daily steroid excretion in individual infants. Results from pooled urine are only of limited value in the assessment of adrenal function.

Dehydroepiandrosterone has been detected in pooled urine from premature infants but not in pooled urine from full-term infants, although trace amounts have sometimes been found in the urine from individual full-term babies. The finding of dehydroepiandrosterone in premature-infant urine is in keeping with the evidence of Eagle.[12] Francis et al.[13] have been unable to detect this substance in the pooled urine of full-term infants during the first 4 days after birth but have shown that it is present in meconium. They postulate that the secretion of dehydroepiandrosterone may be a fœtal trait. The significance of large quantities of Zimmermann-reacting unknown substances in infant urine is not yet appreciated. They are proportionately less important in maternal than in infant urine and it is possible that they may be derived from the fœtal cortex. The altered pattern of excretion of C_{19} steroids in pregnancy has been described by others [14 15] but its cause remains obscure.

The pattern of excretion of C_{21} steroids appears to be similar in premature and full-term infants, and the few individual infants studied so far have not shown significant differences between the two groups in the quantitative excretion of corticoids. It may be that most of the C_{21} steroids excreted by infants in the first days of life are maternal in origin. Migeon et al.[16] have demonstrated the transfer of cortisol across the placenta from mother to fœtus and it is known that blood levels of cortisol are high in the third trimester of pregnancy.[14] The stress of

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labour causes a further rise in cortisol output and this is demonstrated by the results in the table showing the high urinary corticoid output of mothers in the 24 hours following normal delivery. In the urine of both premature and full-term infants the output of corticosterone is significantly greater than the output of cortisol. This contrasts with the pattern of excretion of these compounds in adults.

The increased excretion of 6-beta-hydroxylated compounds in the urine of late pregnancy and in the urine of newborn infants has been described by others.[17–19] Although hydroxylation at C-6 has been shown to be possible in adrenal tissue,[20] it is probable that, in the adult at least, 6-hydroxy compounds are not secreted as such but are derived mainly from the metabolism of cortisol, and become increasingly important when blood levels of this precursor compound are high. Being relatively soluble, they provide an alternative pathway for excretion of cortisol when the major route, which depends on conjugation of metabolites formed in the liver, is unduly taxed.[18] This situation occurs in the period immediately following delivery and the hypothesis is supported by the high urinary output of these compounds at this time.

The importance of the unknown compounds found in all fractions and as yet unidentified remains to be elucidated.

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EFFECT OF ANGIOTENSIN (HYPERTENSIN OR ANGIOTONIN) ON URINE FLOW AND ELECTROLYTE EXCRETION IN HYPERTENSIVE PATIENTS

BECAUSE opinions differ on the role of the renin/angiotensin (hypertensin or angiotonin [1]) system in human hypertension,[2] we decided to study the effects of infusing angiotensin into patients with high blood-pressure.

In subjects with normal blood-pressure (fig. 1), angiotensin is known to have marked effects on renal function.[3 4] But, in contrast to the antidiuresis seen in the normotensive subjects, a diuretic effect was frequently observed in hypertensive patients. We later found that this response was in agreement with the findings of Nijensohn.[5]

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THE INVESTIGATION

Methods

Patients were given 750-1000 ml. of water to drink in the hour preceding the experiment, and this water load was maintained throughout by oral replacement equal to urine volume.

In most experiments urine was passed in the normal way, and, when the urine flow-rate was steady, angiotensin (synthetic asparginyl, val. 5 octapeptide Ciba, Schwyzer and Sieber [6]) was infused into an arm vein. Each infusion lasted twenty to thirty minutes, at rates of 1–3 μg. per minute, this amount being sufficient to increase the blood-pressure some 20–30 mm. Hg. The only symptoms during the infusions were a slight headache in one patient and abdominal pain in another.

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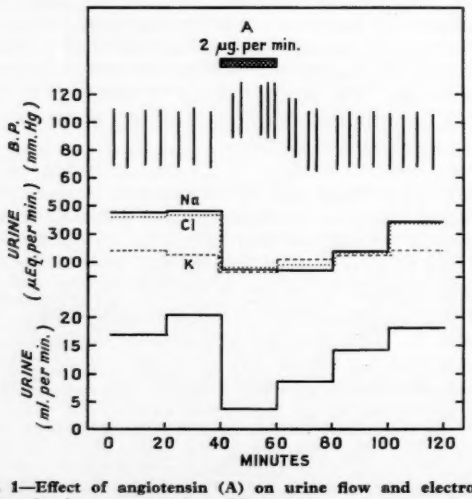

Fig. 1—Effect of angiotensin (A) on urine flow and electrolyte excretion in a normotensive subject.

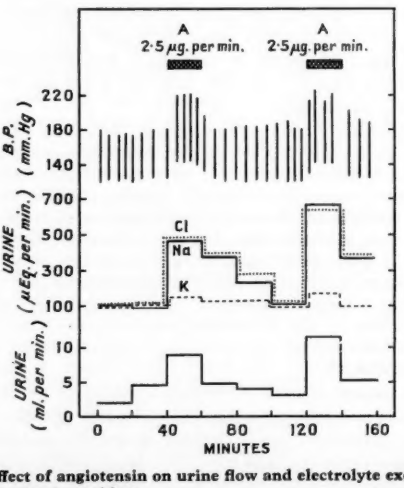

Fig. 2—Effect of angiotensin on urine flow and electrolyte excretion in a hypertensive subject.

Clearances of inulin (In) and *p*-aminohippurate (P.A.H.), and the concentration of urinary electrolytes, were determined by standard methods.

Patients

21 patients with hypertension of varied ætiology (6 renal-artery stenosis, 6 essential, 5 chronic pyelonephritis, 1 coarctation, 1 phæochromocytoma, 1 Cushing's syndrome, 1 tuberculous pyelonephritis) were infused. The resting blood-pressure ranged from 160/100 to 250/150 mm. Hg, and 16 of the patients were male.

Results

In contrast to the antidiuretic effect in subjects with normal blood-pressure (fig. 1), the response was diuretic in 16 of the 17 patients with resting diastolic pressures greater than 120 mm. Hg. There was a corresponding increase in the excretion of sodium and chloride (fig. 2) whereas the normal subject shows a decrease—3:4 (fig. 1).

During most of the diuretic responses the inulin clearances remained essentially unaltered (fig. 3a), but in 2 patients they increased, considerably. As a rule, the clearance of P.A.H. was slightly reduced (fig. 3a), but in 3 patients it increased substantially. In normal subjects the clearances of both inulin and P.A.H. are reduced by angiotensin infusions (fig. 3b).[3,4]

Conversion from Diuretic to Antidiuretic Response

The high blood-pressure in 4 of these patients was restored to more normal levels by surgical treatment (conservative surgery for unilateral renal-artery stenosis in 2 patients, and nephrectomy in 2 others).

Fig. 4 shows conversion to the normal anti-diuretic response in one of these patients after thromboendarterectomy for renal artery stenosis. A similar reversal was seen in the other 3 patients treated surgically and also in 1 whose blood-pressure was satisfactorily controlled by treatment with hypotensive drugs. This change in response did not occur immediately after the high blood-pressure was lowered acutely (3 patients) but only after the more normal level had been maintained for several months.

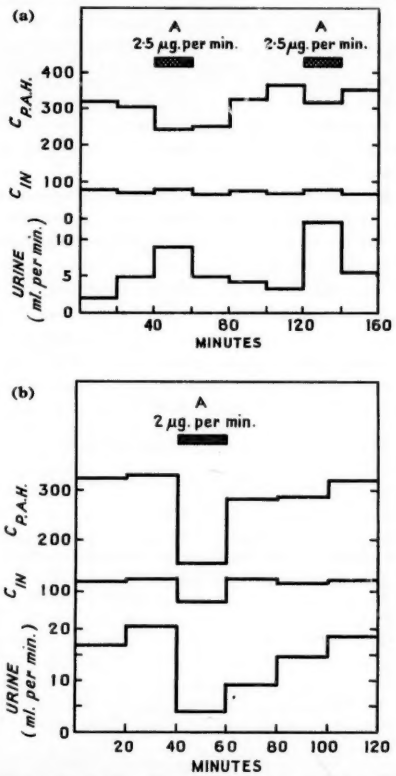

Fig. 3—Effect of angiotensin on clearance of inulin (C_{In}) and *p*-aminohippurate ($C_{P.A.H.}$) in (a) a hypertensive patient, and (b) a normotensive subject.

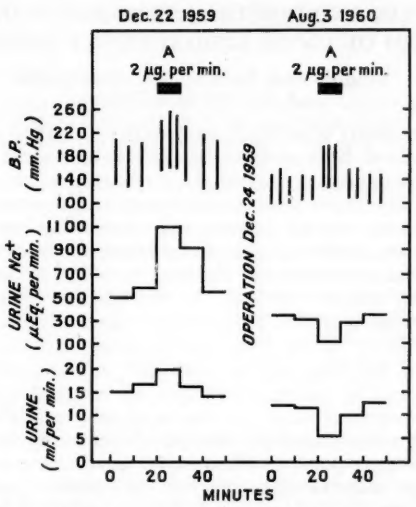

Fig. 4—Conversion from diuretic to antidiuretic response after renal thromboendarterectomy.

DISCUSSION

Some of the diuretic responses were associated with a definite increase in inulin clearance, and this provides a possible explanation for the effects observed. However, in 2 patients the inulin clearance was slightly reduced during the infusion, suggesting that the diuresis in these cases was due to a failure of tubular reabsorption.

Other infusions were associated with essentially unchanged inulin clearances, and in these a direct tubular effect is again possible although it should be remembered that only small changes in glomerular filtration-rate are needed to produce large percentage changes in urinary excretion.

The marked fall in the inulin and P.A.H. clearances which has been constantly observed during angiotensin infusions into normotensive subjects has not been seen in patients with high blood-pressure. This suggests that the intrarenal vessels in hypertensive patients have become less sensitive to the direct constrictor action of the drug. This change in reponse may be a result of the hypertension itself, since after the blood-pressure has been maintained at more normal levels angiotensin may again produce intrarenal vasoconstriction, as shown by a fall in the inulin and P.A.H. clearances.

SUMMARY

Angiotensin infused into subjects with normal blood-pressure produces an anti-diuresis, whereas a diuresis with increased sodium and chloride excretion occurs in most patients with severe hypertension.

It is suggested that the intrarenal vessels in hypertensive patients are less sensitive to the constrictor action of angiotensin, although a decrease in reabsorption produced by a direct tubular action of angiotensin is not excluded.

If the blood-pressure is lowered and then maintained at a more normal level, angiotensin again produces an antidiuresis accompanied by a fall in the clearances of inulin and *p*-aminohippurate.

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INSULIN AND INSULIN ANTAGONISTS IN THE SERUM OF UNTREATED JUVENILE DIABETES

Studies with Isolated Rat Diaphragm and Rat Adipose Tissue

THE effects of serum from diabetics of various clinical types have been extensively studied by means of the glucose uptake of isolated rat diaphragm, as an insulin assay. A number of workers have reported that the serum of severely ketosed patients has significantly less effect on glucose uptake than that derived from normal people.[1–5] By contrast, preliminary observations of the oxidation of labelled glucose to $^{14}CO_2$ by rat adipose tissue as a measurement of insulin-like activity suggested normal or even raised serum levels in untreated diabetics with ketosis, including patients with early juvenile diabetes.[6] It seemed of interest, therefore, to compare (on both tissues simultaneously) the effects of samples of the same serum from untreated juvenile diabetics, using these metabolic responses. The results suggest that in early juvenile diabetes there may be considerable quantities of insulin circulating, though muscle and adipose tissue may respond differently to it.

METHODS

The diabetic patients we studied had never had insulin or oral hypoglycæmic therapy. Random samples of venous blood, taken on attending a diabetic clinic, were assayed for insulin activity. The effects of serum on glucose uptake by rat diaphragm were determined by the method of Randle,[7] except that Krebs-Ringer bicarbonate buffer was used in place of that of Gey and Gey.[8] The insulin-like activity of serum on adipose tissue was assessed by the effects on the oxidation of 1-^{14}C glucose to $^{14}CO_2$ by the method of Martin et al.,[9] as modified by Renold et al.[10] The results were expressed as microunits of insulin-like activity per ml. of serum, by reference to the effects of appropriately diluted ox-insulin standards. Reference to crystalline insulin standards is an essential part of the adipose-tissue assay design. Insulin activity in muscle was expressed as the difference in glucose uptake between diaphragms incubated in serum and diaphragms incubated in buffer, without reference to standards. Reasons for regarding such effects as due to circulating insulin have been presented in detail.[11] The serum concentration used was 25% for experiments with both tissues.

RESULTS AND DISCUSSION

The results of examining samples of serum from normal individuals and from juvenile diabetics are shown in the table. The mean additional effect of serum from normal people on glucose uptake of isolated rat diaphragm is greater than that of serum from the diabetics, and this difference is statistically significant ($P < 0.05$). These results contrast strikingly with those from identical samples of serum tested by rat adipose tissue. Using this tissue the mean effect of the diabetic serum is about twice that of normal serum ($P < 0.05$). Such differences between the serum of normal people and of untreated juvenile diabetics have also been observed when more samples were tested on adipose tissue alone (Steinke, unpublished observations). It seems likely that these effects with adipose tissue are due to insulin, because they can be abolished by pretreating the serum with reduced glutathione.

Further evidence that the serum of juvenile diabetics contains insulin has been derived from protein-fractionation studies. Using fractions obtained by column electrophoresis, it can be shown that both the albumin fraction and the β and γ globulin fractions stimulate the glucose uptake of isolated rat diaphragm in a quantitatively similar way to the same fractions from normal serum. The material which stimulates glucose uptake in diaphragm behaves like insulin on dialysis (Taylor, unpublished observations); reasons for regarding similar effects in protein fractions of normal serum as due to insulin have been reported.[11 12] Similar results for the effect of protein fractions of serum from ketosed diabetics on rat diaphragm have also been reported.[13]

CONCLUSION

This evidence suggests that insulin may be present in considerable quantities in the serum of untreated juvenile diabetics, at least in the early stages of their disease. The clinical observation that many of these patients later show a substantial degree of remission is in keeping with this possibility.

The discrepancy between the results obtained using adipose tissue and those using rat diaphragm, when diabetic serum is assayed for insulin and compared with normal serum, requires further comment. It seems possible that insulin in the serum of ketosed diabetics is ineffective with regard to muscle because of circulating antagonists.[1 2 4] Adipose tissue need not respond to such an antagonist; and, in the presence of such substances, each tissue might respond differently to insulin. This point has still to be tested by more direct experiments

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EFFECT OF SERUM (25%) FROM UNTREATED EARLY JUVENILE DIABETICS ON METABOLIC ACTIVITY IN ISOLATED RAT DIAPHRAGM AND IN ADIPOSE TISSUE

Normal subjects	Effect with rat diaphragm*	Effect with rat adipose tissue†	Diabetic patients	Blood-sugar (mg. per 100 ml.)	Urine ketones	Effect with rat diaphragm*	Effect with rat adipose tissue†
1	+0·8	..	1	384	4+	+0·6	..
2	+1·8	..	2	340	4+	+0·8	191
3	+1·0	31	3	300	4+	+0·5	113
4	+1·6	60	4	400	4+	+0·5	140
5	+0·8	58	5	410	4+	+1·0	300
6	+1·1	71	6	259	4+	+0·6	138
7	+1·0	77	7	420	2+	+0·6	69
8	+0·6	170					
Mean ±	1·1	78	..	..	..	0·7	159
S.E.M.	±0·15	±20	..	..	..	±0·07	±33

*Results expressed as difference in glucose uptake between diaphragm incubated in buffer and serum, and in buffer alone. Differences are derived from experiments using 6–8 diaphragms, and are expressed as excess mg. glucose utilised per g. wet diaphragm per hr. incubation.
†Oxidation of glucose 1-^{14}C to $^{14}CO_2$ with reference to effects of crystalline ox-insulin standards, expressed as microunits per ml.
Ratio diabetics/normal: by rat adipose tissue = 2·0, by rat diaphragm = 0·6.

using identical metabolic effects of insulin in the two tissues.

We wish to thank the staff of the Joslin Clinic for their cooperation in enabling blood samples to be taken from their patients. This work was done during the tenure of a research fellowship from the American Diabetes Association, held by J. S., and a Wellcome Research Travelling Fellowship, held by K. W. T. These studies were supported in part by a grant from the Lilly Research Laboratories, Indianapolis, Indiana.

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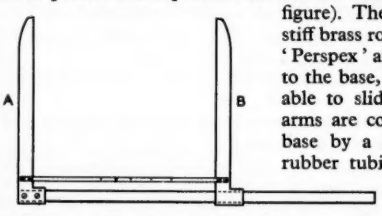
New Inventions

A CALLIPER FOR SITING THE PRECORDIAL LEADS IN ELECTROCARDIOGRAPHY

MOST electrocardiograph technicians place the precordial electrodes by eye alone; and many have never actually measured the true position of the midclavicular line. To test the magnitude of error in practice, two experienced technicians were asked separately to mark on the chests of twenty male patients the positions at which they would place lead V_4. The true position of V_4 was then determined by measurement. The first technician had a mean error of 2·41 cm. too far laterally, with a maximum error of 3·5 cm. The second had a mean error of 1·05 cm. too far medially, with a maximum error of 2·5 cm.

Thus it appears that large errors are possible. On a single tracing this is most likely to be misleading as regards the determination of cardiac rotation. A greater danger is that in serial tracings changing the position of the electrodes may give a false appearance of a changing pattern, possibly leading to a diagnosis of myocardial injury.

A simple calliper has therefore been designed to provide a more precise and repeatable method for siting leads V_{1-4} (see figure). The base is made of stiff brass rod. There are two 'Perspex' arms, one (A) fixed to the base, and the other (B) able to slide along it. The arms are connected near the base by a length of 3-mm. rubber tubing on which are marks corresponding to the midline and to the positions for V_{1-4}. The positions for V_1 and V_2 lie 16% of the distance from the midpoint to the nearest arm; V_4 lies 64% of the distance from the midpoint to arm B; and V_3 lies midway between V_2 and V_4.



In use the calliper is laid astride the patient's chest, with one arm in each axilla. The base lies about 1 in. below the xiphisternal joint, with the midpoint of the rubber tubing in the patient's midline. The electrode is then placed on the chest vertically above the appropriate mark on the tubing.

When this calliper was applied to the chests of the twenty patients already tested, the mean error for the crucial lead, V_4, was 0·05 cm. too far laterally, with a maximum error of 1·5 cm. Perhaps of greater importance than the error on any one occasion is the fact that the positions can be closely repeated on successive occasions, even with different observers. The method is simple, occupying only a few seconds.

The cost of making the calliper was met from a special fund of the United States Public Health Service, administered by the joint U.S.–U.K. Board for Research in Respiratory and Cardiovascular Diseases.

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Reviews of Books

Peptic Ulceration

A Symposium for Surgeons. CHARLES WELLS, F.R.C.S., professor of surgery, University of Liverpool; JAMES KYLE, F.R.C.S., senior lecturer in surgery, University of Aberdeen. Edinburgh: E. & S. Livingstone. 1960. Pp. 260. 42*s.*

THERE is a Liverpool-Belfast-Sheffield-Glasgow axis concerned with peptic ulceration along which is evident a special interest in the subject and a specialised approach towards research. This book presents the Liverpool-Belfast wing, with intrusions as welcome as the rest from Aberdeen and Edinburgh in competent chapters on epidemiology and ætiology. The surgical burden in the technical sense is carried by the senior author, whose experience and approach to the subject make him particularly suitable for this contribution; despite the weight of his authority he has not allowed his contribution to get out of balance with the rest. From the Belfast end come two chapters on the effects of gastrectomy and one on recurrent ulceration written with the aplomb to be expected from Prof. R. B. Welbourn, a master of these subjects.

An opportunity seems to have been missed by those who contributed the chapter on pyloric stenosis; how welcome would have been the title duodenal stenosis, which they, as surgeons, must know is vastly more common than pyloric stenosis, a term confusing to students and a misnomer from the days when there was no gastric surgery to speak of and therefore no opportunity to see the real state of affairs in duodenal ulceration. And can they really believe that spasm of the pylorus is a cause of the obstructive syndrome implied by the misnomer pyloric stenosis?

It is tempting to use peptic ulcer as a collective term to save the trouble of speaking of duodenal and gastric ulcer. But as long as we continue to use this term we shall flounder in misconceptions. And this approach predominates in this book, which accepts gastric and duodenal ulcers as to all intents and purposes one and the same. The dogma is emphatically stated at the outset of the chapter on ætiology: the essential mechanism in the formation of a peptic ulcer is the digestion of the alimentary mucosa by acid and pepsin. So, of course, peptic ulcer it must be—but is it, really? The extensive research on this subject over so many years has yielded much information about acid but little about ulcer, perhaps because we have been mesmerised subconsciously by the term *peptic* ulcer and are barking up the wrong tree.

But this is no discredit to the authors and contributors; they are reflecting the customs of their day; they do not wish to challenge. But they do wish to inform. Even the index is educative, for there (and nowhere in the text where it is referred to in its usual guise) will be found the nesidioblastoma—a good one to try out at the tea-table sometime.

The Single Woman

LAURA HUTTON, B.A., M.R.C.S., late physician, Tavistock Clinic, London. Barrie and Rockliff. 1960. Pp. 132. 12*s.* 6*d.*

THIS thoroughly revised and expanded version of a book which has been well known in medical circles for some years was first published in 1935 under the title, *The Single Woman and her Emotional Problems.* Since then the number of "surplus" women, once estimated at about 2 million, has greatly diminished. Moreover, single women are likely nowadays to be better prepared to cope with problems of emotional and sexual adjustment. The enormous increase in opportunity, freedom, and accessibility of knowledge during the past twenty-five years has to some extent altered the needs and difficulties of single women. This new edition is addressed to the woman herself rather than to her doctor, but there is much in it that should interest not only doctors but all who are interested in the world about them.

Dr. Hutton says that the single woman can never feel a sense of complete fulfilment, and nowadays, since it is widely accepted that total fulfilment requires complete sexual satisfaction and also childbearing, the single woman is likely to be

even more conscious of the shortcomings in her life than she was formerly. Her basic emotional problem is loneliness. This is not always perceived but in fact women are peculiarly unfitted to tolerate loneliness because love for them is more all-embracing and continuous than it is for men. Once middle-age approaches and prospects of marriage are small, the chief and most satisfactory outlet for the single woman lies in friendship. Dr. Hutton believes that the experience of friendship is bound to be of such great significance in the single woman's life, and at the same time can present so many pitfalls, difficulties, and disappointments, that she has devoted a great part of the book to it, in the hope of helping women to understand its many aspects. The joys and frustrations inherent in emotional friendships between women are thoroughly and helpfully analysed.

She points out that many single women are perfectly "normal" in every way. Many others are immature and "perpetual adolescents". Dr. Hutton shows great understanding of these people and emphasises that the spreading of knowledge concerning the findings of modern psychology has laid so much emphasis on *immaturity* revealed in childish relationships and in so-called "inhibitions" that many women now feel the same sense of inferiority and guilt if labelled "immature" or "inhibited" as they would in the old days if they had been called "forward" or "fast" or even "demonstrative". In reality, immaturity, in the sense in which the word is used here, is compatible not only with sensitivity and intelligence but also often with creative ability. In fact a "mature" person may be very much more ordinary, not to say dull, than a psychologically speaking "immature" one. But emotional friendships in these immature women can be fraught with disaster.

The book makes some sensible and practical comments on sublimation, which "does *not* mean just keeping your mind and body busy with other things". It is emphasised that masturbation may be necessary and desirable for physical relief but that it will not bring emotional satisfaction: it will be harmful only if the woman becomes preoccupied by it and is consumed with guilt. There is a short section on extramarital affairs and the difficulties associated with them. Non-sexual friendships with men are also briefly discussed and dismissed as impracticable. The arousal of sexual feelings in friendships between women is quite common and natural and often present without either party being aware of it. Dr. Hutton speaks of it as "one of the psychological and sociological problems which quite naturally arise when the women in a monogamous community significantly outnumber the men". Increasing awareness and freedom of discussion of topics connected with homosexuality has not had an entirely beneficial effect. It has led to an increased tendency on the one hand of the so-called "normal" to speculate, ridicule, or condemn, and on the other hand of the sexually inverted to make exaggerated claims for consideration and sympathy.

This important book, well written and thoughtful, deserves a wide readership.

Hypothermia in Surgical Practice

K. E. COOPER, M.SC., M.B., Medical Research Council's group for research on body temperature regulation, department of the regius professor of medicine, Radcliffe Infirmary, Oxford; D. N. ROSS, B.SC., M.B., F.R.C.S., consultant thoracic surgeon, Guy's Hospital, London. London: Cassell. 1960. Pp. 116. 18*s*. 6*d*.

THIS short book fills a gap in cardiac and neurosurgical literature. The authors and their contributors all have wide experience of hypothermia, and they have covered the subject in a remarkably compact book. They aim to help those starting to use hypothermia clinically, to illustrate the techniques and point out the pitfalls. The first three chapters on physiology, pharmacology, and metabolic problems are packed with information, so the text is rather staccato and the matter somewhat indigestible, though for reference they are admirable. They will be most help when read a second time after some practical experience.

The succeeding chapters on techniques and applications are short and easily absorbed. With the increasing application of a combination of cardiopulmonary bypass and hypothermia of various depths, the later chapters are relatively more important, and fairly summarise the position early last year; but obviously these chapters cannot be a guide to these techniques for beginners as the earlier ones are for hypothermia alone. Selective cooling of the heart during perfusion might be discussed more fully.

The descriptions of the techniques of surface and bloodstream cooling are impartial, and the reader is left to decide for himself which he prefers. The list of references is wide and illustrates the care the authors have taken to cover the subject. They should be congratulated on compressing so much information into a book of this size, and not only beginners but also the more experienced will profit from it.

Infant Foods and Feeding Practice

HERMAN FREDERIC MEYER, A.B., M.D., associate professor, department of pediatrics, Northwestern University Medical School, Chicago. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 332. 78*s*.

THIS reference book covers in some detail the more complicated aspects of infant feeding. Set out here and well documented is much information about an infant's nutritional requirements and the pros and the cons of the various kinds of baby foods available in the United States, where there are some 300 different types of milk sold for babies. Anyone troubled by problems of protein/aminoacid ratios, carbohydrate additives and modifiers, or "low curd tension" will find the answer here.

The book will help those doing research into the nutritional requirements of infants, and also anyone who believes that the exact contents of a baby's bottle should be known in detail or that small variations are of vital importance. But those who hold that infant feeding is largely a question of "when he is hungry, give him a bottle of milk" will probably be uninfluenced by the book. Those who believe that the mother-child relationship is an important aspect in infant feeding will be disappointed since the book contains very little on this topic and there is no entry "mother" in the index.

It is doubtful whether, in the United Kingdom, it will be widely read by those for whom it is intended—residents, general practitioners, medical students, and pædiatricians. It makes the whole business of normal infant feeding seem so complicated.

Ciba Foundation Symposium on Cellular Aspects of Immunity (London: J. & A. Churchill. 1960. Pp. 495. 60*s*.).—This book, edited by Dr. G. E. W. Wolstenholme and Miss Maeve O'Connor, contains the papers and verbatim discussions of a meeting of distinguished immunologists on June 3–5, 1959. A panel discussion was held on the clonal selection theory of antibody production propounded by Sir MacFarlane Burnet and Dr. J. Lederberg, and much of the discussion centred on the lineage of immunologically competent cells. This is not a book for the novice, but for those specially interested in immunity it is fascinating. There is a lot of interesting new work described and reviewed and subjected to critical examination by leading experimentalists. Particularly interesting accounts were given of the morphology and fine structure of the immunologically competent cell. The theories of Burnet and Lederberg are exposed to penetrating criticism, and suggestions emerge for fresh experimental approaches.

A Proposed Standard of Nomenclature of Human Mitotic Chromosomes (Supplement to *Cerebral Palsy Bulletin*, vol. 2, 1960. Obtainable from the National Spastics Society, 28, Fitzroy Square, London, W.1. 5*s*.).—This is a convenient and elegant reproduction of the statement prepared by a study group which met in Denver last spring to formulate an agreed system of nomenclature for human chromosomes, in the hope of eliminating the confusion arising from the various systems used by different workers. Two large and clear photomicrographs are included.

THE LANCET

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Progress in 1961?

BECAUSE no week passes without some advance in medicine, we tend to think of ourselves as the most progressive of professions. Yet to some outsiders we seem the most static. A brilliant symposium on "the crisis in American medicine",[1] which contains comments as applicable to Britain as to the United States, opens with an attack on organised medicine as an obstacle to reform. The writer, Mr. EDWARD T. CHASE, agrees that in theory there is no objection to our organisations making sure that there are not too many doctors, and that those admitted to the fraternity abide by the rules; but he argues that in practice the system controls a good deal more than medical excellence. Though we in this country may reasonably suppose that acceptance of the National Health Service has put our adaptability beyond question, the resistance of the British profession towards further change may in fact be all the greater because it feels that it has already done so much. With so many doctors still thinking wistfully about the past rather than constructively about the future, there is always a welcome for the returning status quo. Yet in Britain, as in America, few of the problems of 1961 are likely to yield to the solutions of 1939—attractive though these may seem in retrospect.

Sooner rather than later, profession and public will have to answer Professor RUTSTEIN'S question[2] "Do you really want a family doctor?"; for, though the N.H.S. assumes the existence of such a person, it has not yet done much to promote his adaptation to our times, and thus ensure his future. Many of the hospital teachers who train future family doctors still think that all that matters is that these should be able to screen their patients so that anyone seriously ill is brought to the hospital in good time. Unfortunately, too, many of the doctors themselves have acquired their teachers' opinion. But, if that is their essential function, there is probably no reason, in a small country like ours, why they should maintain their professional autonomy: in Britain, as elsewhere, they may sooner or later find themselves superseded by motile members of hospital groups. The case for the independent general practitioner, it has been argued,[3] is that he is, or should be, a personal doctor; and on that criterion the majority of the general practices of today would not satisfy an independent examiner, if only because they do not give their patients enough time. Though LAFITTE and SQUIRE'S prediction that Britain will soon be short of doctors was one of the most important calculations published in this journal last year,[4] the public, having "tried the experiment", have long been well aware that there are not enough doctors to give them the kind of personal help they want.

In the U.S.A. the shortage of doctors is well recognised as part of the crisis of medicine: quite obviously the existing system of medical education cannot produce the great numbers of new doctors who are thought to be needed. But RUTSTEIN[2] is at least equally exercised by the distribution of those who *are* trained—that is to say, by the drift away from family practice:

"Our medical schools are in danger of forgetting their traditional objective: to provide you with ample medical care of constantly rising quality. This requires above all a continued high standard of scientific medicine. But complete medical care means more than the sum of the services provided by specialists, no matter how highly qualified. It must include acceptance by one doctor of complete responsibility for the care of the patient and for the co-ordination of specialist, laboratory and other services. Within a generation, if the present situation continues, few Americans will have a personal physician do this for them."

Only the family doctor can provide coordination and continuity of medical care: "and eventually—if the public demand is strong enough—medical educators will accept the responsibility for training him". The proposal made by RUTSTEIN, and by one or two other American reformers, is a proposal that will no doubt be rejected reflexly by the profession both in the States and here: it is that in medical schools the course of study for practitioners should diverge from that of research-workers and specialists. Believing that future specialists should continue with the present programme, with much basic science, he thinks that, for the student interested primarily in providing medical care, a new curriculum should be designed, in which the art of medical practice would yet be based on a solid scientific foundation:

"This course of training would include all the basic medical sciences needed to interpret the natural history of disease, to care for minor illnesses with drugs or by simple surgical procedures, and to screen seriously-ill patients who need to be referred to specialists. Thus the new curriculum would be soundly based on medical science, in a school where the student is in close contact not only with clinical teachers but also with research workers and specialists. Above all, we must not slump back into the evils of the pre-Flexner era, where students were cut off from the scientific-basis for medicine."

To recommend diverging curricula for the personal doctor and the hospital doctor may seem retrogressive; for is not common education the strongest remaining bond of unity in our already disunited profession? But Dr. BALINT'S article on p. 40, though written from a different standpoint, is similar in urging the recognition of two different kinds of medicine; and it shows how far hospital medicine, with its insistence on "precise" diagnoses, is failing to give patients the help they could be given. The alienation of doctors from patients comes at a time, says GREENBERG,[5] when "the traditional

1. Special Supplement to *Harper's Magazine*, October, 1960.
2. Rutstein, D. D. *ibid.* p. 144.
3. Fox, T. F. *Lancet*, 1960, i, 743.
4. Lafitte, F., Squire, J. R. *ibid.* 1960, ii, 538.
5. Greenberg, S. *Harper's Magazine*, October, 1960; p. 132.

sources of support, such as family and church, have weakened or broken down" and people want more, rather than less, personal attention from their doctors. Are we sure of the advantages of a training which ignores so much that will be necessary, and emphasises so much that clearly will not?

In hospital, likewise, the advance of specialisation may necessitate radical change. At a symposium in Newcastle which we hope to report shortly, admission of patients under the care of a single consultant was criticised on the ground that nowadays this consultant is often a person of narrow interests, using his beds mainly for the practice of a few techniques. Even if the patient is seen by other members of the staff, he commonly feels that, among the experts, nobody is really looking after him as a whole—planning his hospital care so that everything necessary is done expeditiously, both while he remains in bed and afterwards through reablement. Would it not be better (the symposium was asked) if the patient were admitted not under a single specialist but under a group? And, if so, should not responsibility for him be delegated by the group to one of its younger consultants—usually, perhaps, a physician rather than a surgeon—who would look after him personally, seeing him at least once a day and keeping in touch with the practitioner who sent him in? The highly expert would still use their skills of operation or consultation; but the patient, more often than now, would have a doctor of his own in hospital just as he has—or ought to have—a doctor of his own outside. (That, when they exist, hospital doctor and home doctor should work together rather than separately is now agreed by everybody. All we need is some means of ensuring that they regularly do.[3])

Thus, to compensate the patient for its specialisation, the profession may have to alter its concept of general practice and modify some of its customs in hospital. But the changes of the world around us call also for a wider view of our responsibilities. In some ways Central Africa and the Far East are now nearer London than Yorkshire and Westmorland were in the 17th century; and, if we go on thinking of medicine as something chiefly important in these little islands, the kindest thing that history is likely to say about us is that we suffered from an excessive and ill-timed revulsion from Empire-building. "For generations", said a recent white-paper,[6] "British men and women have left their homes to live and work overseas in the service of the Governments and peoples of many lands"; yet somehow, since the second war, in our profession as in the population at large, security has been given too high a value; so that even senior men, who ought to know a great deal better, are inclined to draw their blinds on the alarming world and beg their juniors not to risk going out of doors. What exactly should be done to make our National Health Service less of a bar to international health service is a matter for further thought. But whatever is done will be of little use unless there is also a different attitude in our profession itself, which should see its responsibilities, in 1961, as something far wider than the provision of medical care for the people of Great Britain.

6. Service with Overseas Governments. Cmnd. 1193. H.M. Stationery Office, 1960.

Postanæsthetic Respiratory Insufficiency

SOME five years ago there was great interest in the "relaxant apnœas". This term unfortunately was inaccurate, for it covered two quite distinct types of case—namely, those in which genuine apnœa was present, and those where the basic trouble was not absence of breathing but intractable respiratory depression. The mechanisms in the first type have now been elucidated. Some cases are in no way due to the relaxant. They are due rather to direct or reflex depression of the respiratory centre: the action of drugs, such as the combination of thiopentone and morphine, or simple acapnia are the likeliest causes. Another type is due to idiosyncrasy to suxamethonium, traceable often to a deficit of sufficient of the appropriate plasma-cholinesterase to hydrolyse the relaxant.

The second type was originally described under the title of neostigmine-resistant curarisation. In the light of more modern knowledge it is doubtful whether in fact all the cases reported under this title qualify for the description. Apparent prolongation of the effect of curarising drugs beyond their normal period of action was, and probably still is, not infrequent, but, as is now evident, this clinical syndrome may reflect any of several disease states. Administration of *d*-tubocurarine is known to produce profound and often neostigmine-resistant paralysis in patients with myasthenia gravis.[1] It is also known that the administration of an anæsthetic to a patient with dystrophia myotonica is liable to be followed by persistent respiratory insufficiency. This disturbance was originally thought to be a specific response of the myotonic to thiopentone, but recently it has seemed that morphine may have the same effect.[2] Finally, carbon-dioxide narcosis gives rise to a syndrome of respiratory insufficiency (characterised by unconsciousness, inadequate tidal volume, and tracheal tug), which is not readily distinguished by ordinary clinical examination from curarisation.[3 4] Indeed, anæsthesia and operation are associated with so many factors that tend to disturb carbon-dioxide elimination that such disturbance may be the commonest cause.

These established facts are supplemented by laboratory observations on the action of myoneural blocking-agents which may have a bearing on persistent respiratory insufficiency after anæsthesia. Thus it has been shown that temperature influences the intensity of the block produced by a relaxant drug.[5] Decamethonium, and presumably other depolarising blockers, are more active at lower body-temperatures, while the intensity of the effect of *d*-tubocurarine becomes progressively less as the temperature of the muscle on which it acts falls. This observation is unlikely to be important in relation

1. Gray, T. C., Halton, J. *Brit. med. J.* 1948, i, 784.
2. Kaufman, L. *Proc. R. Soc. Med.* 1960, 53, 183.
3. Scurr, C. F. *Brit. med. J.* 1954, i, 565.
4. Gray, T.C., Fenton, E. S. M. *ibid.* p. 820.
5. Bigland, B., Goetzee, B., Maclagan, J., Zaimis, E. *J. Physiol.* 1958, **141**, 425.

to unexpected prolongation of the action of decamethonium, since this drug is nowadays used rarely in large dose and virtually never when hypothermia is induced. It may, however, explain re-curarisation during rewarming in a hypothermic patient to whom neostigmine has been administered apparently successfully as an antidote to *d*-tubocurarine. Work on local cooling of muscles during thoracotomy [6] has indicated that the temperatures of the intercostal muscles may fall quite profoundly in normothermic patients while the thorax is open. Presumably the temperature will take some time to rectify itself after operation, and it is at least possible that if the curarisation of these muscles were reversed while they were cold they might become paralysed again as their temperature rose.

The mixing of relaxant drugs of different types is regularly named as a cause of unexpected prolongation of their action. Yet, apart from some in-vitro observations,[7 8] there is no convincing evidence that the administration of an induction dose of suxamethonium for intubation, previous to the use of a non-depolarising relaxant for the operation itself, ever causes serious difficulty; but if the myoneural block produced by suxamethonium is maintained for some time it gradually loses its depolarising characteristics and takes on instead those of a non-depolarising agent.[9] CHURCHILL-DAVIDSON [10] has clearly shown that this disturbance, known as dual block, is reversible by neostigmine. Dual block therefore is to be regarded, not as a cause of persistent respiratory insufficiency, but rather as an accompaniment (though by no means an inevitable one) of the unexpected prolongation of the action of suxamethonium. But there is no denying that repeated changes of myoneural blocker,[11] or occasionally the prolonged action of suxamethonium alone, can give rise to a persistent block which is not reversed by neostigmine,[9 12] and for this reason mixtures of relaxant drugs should be avoided. Even a final dose of suxamethonium at the end of the operation in order to provide relaxation for closure may not be safe.[13]

Another presumptive cause of persistent respiratory insufficiency after anæsthesia is a myoneural block produced by neostigmine given in generous dose in an attempt to reverse seemingly obstinate curarisation produced by a non-depolarising blocker. By itself this agent can produce myoneural block of the depolarising type,[14] but in view of the known antagonism between the two groups of myoneural blocking-agents it is doubtful whether neostigmine would still produce such a block after *d*-tubocurarine or a like drug had been given. The fact remains that antidotal doses of neostigmine are not usually allowed to exceed 5 mg. Finally, there is yet another presumptive cause of persistent respiratory insufficiency following administration of relaxant drugs. Both hyper- and hypo-potassæmia can be accompanied by muscular paralysis: and it is not surprising that earlier workers on this subject [15–17] inclined to such an explanation. In fact, enough cases of persistent respiratory insufficiency have now been described in which the serum-potassium was normal to make it very doubtful whether this is a common cause of the condition, though certainly it can occasionally be responsible.

Formerly diagnosis of the nature of persistent depression of respiration after anæsthesia depended on therapeutic testing. If the condition responded to non-specific analeptics it was a drug depression; if to specific morphine antagonists, opiates were responsible; if to hyperventilation, it was a carbon-dioxide narcosis. The making of this last diagnosis on a therapeutic test is particularly fallacious, for the first effect of hyperventilation in carbon-dioxide narcosis is temporarily to abolish respiration. The improvement obtained by this measure is noted only when breathing re-establishes itself after artificial ventilation has been stopped.

Exact diagnosis of these cases has been greatly aided by the work of CHURCHILL-DAVIDSON,[18] who has drawn attention to the value of a stimulator not only for demonstrating myoneural block but also for diagnosing its nature. The development of respiratory physiology has placed the direct diagnosis of carbon-dioxide narcosis within the reach of many clinicians. A high pCO_2 is evidence of carbon-dioxide narcosis only where ventilation has been maintained at a normal level from the time at which respiratory insufficiency has been diagnosed. If a patient is allowed to breathe oxygen spontaneously while his respiration is depressed his colour will be maintained but secondary accumulation of carbon dioxide will result. In consequence such a patient will have a high pCO_2, a slightly raised blood-pressure and pulse-rate, and a flushed face—just like a patient with true carbon-dioxide narcosis. Moreover, determination of the "alveolar" CO_2 will not reveal the true state of affairs if the cause of the carbon-dioxide retention is loss of alveolar permeability from incipient pulmonary œdema—a state which is quite easily produced by over-generous transfusion. The patient with dystrophia myotonica should be recognised by the swan neck, the pale, almost hypopituitary, cast of face, the thinning hair, the cataracts, and perhaps a thyroid operation scar. Such a patient will almost certainly not have recovered normal breathing in reasonable time after an induction.

Just as there have been tremendous advances in the diagnosis of such cases, so also their treatment has been improved. Treatment consists basically in artificial ventilation of the lungs. Because this may need to be continued for many hours a machine is always preferable—particularly if one can be found with a negative phase,[19] which may help to maintain the rather precarious circulatory stability. If myoneural block of

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7. Jenden, D. J., Kamijo, K., Taylor, D. B. *J. Pharmacol.* 1954, **111**, 229.
8. Jenden, D. J. *ibid.* 1955, **114**, 398.
9. Brennan, H. J. *Brit. J. Anæsth.* 1956, **28**, 159.
10. Churchill-Davidson, H. C. *Proc. R. Soc. Med.* 1955, **48**, 621.
11. Hodges, R. J. H., Foldes, F. F. *Lancet*, 1956, ii, 788.
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13. Hodges, R. J. H. *Brit. med. J.* 1957, i, 648.
14. Harvey, A. M., Lilienthal, J. L., Talbot, S. A. *Bull. Johns Hopk. Hosp.* 1941, **69**, 547.
15. Dripps, R. D. *Ann. Surg.* 1953, **137**, 145.
16. Hunter, A. R. *Brit. med. J.* 1956, ii, 919.
17. Foster, P. A. *Brit. J. Anæsth.* 1956, **28**, 488.
18. Churchill-Davidson, H. C. *Lancet*, 1958, i, 776.
19. Gray, T. C. *Brit. med. J.* 1956, ii, 1365.

the non-depolarising type is present edrophonium ('Tensilon') and then neostigmine may be given once; but if this fails to produce immediate and complete recovery it is undesirable to use more. Where one such dose has failed, the only possible course is to continue artificial ventilation until the offending drug is eliminated naturally. Provided the urinary output of fluid continues, intravenous infusion of fairly large amounts of 5% dextrose may hasten this process. The blood-pressure must be maintained, with a noradrenaline drip if necessary. A similar regimen is required in the myotonic patient who fails to breathe adequately after operation.

The patient with carbon-dioxide narcosis requires hyperventilation; and again a machine is best, particularly as it can be difficult to strike a balance between the vigorous ventilation required to wash out carbon dioxide and the associated adverse effects of the positive pressure on the venous return. In addition, the patient may be helped by administration of base to combine with the excess carbon dioxide. Thus sodium lactate can be given intravenously.[20] Recently THAM (2-amino-2-hydroxymethyl-1-1-3 propanediol) has become available for the same purpose [21 22]; and it is probably to be preferred as its administration in quantity need not involve the risk of giving too much sodium.

Provided circulatory stability can be maintained there is no theoretical limit to the period for which artificial ventilation of the lungs can be continued in a case of postoperative respiratory insufficiency; and where there is no irreversible cause, such as cerebral damage produced by anoxia or an intracranial vascular accident, there is no need to despair of the ultimate outcome.

Prospects for a Viral Antibiotic

THE doctor faced with the winter's crop of respiratory-virus infections hardly needs to be told that what is required is a broad-spectrum antiviral substance. Such an agent, if it could be used against nothing but the formidable array [23] of influenza and parainfluenza viruses, adenoviruses, enteroviruses, and common-cold viruses which inhabit our respiratory tracts, would be a boon to the harassed general practitioner. Even more valuable would be a drug which could deal also with systemic virus infections, and particularly with infections of the central nervous system. The prospects in this difficult field of research have been discussed by Dr. IGOR TAMM.[24]

TAMM describes three groups of virus-inhibitory substances with significant selectivity—i.e., ability to inhibit virus multiplication without damaging the host cells. Selectivity of action has always been the basic problem in the search for useful antiviral substances. Viruses borrow their host's foodstuffs, metabolic machinery, and enzymic equipment when they multiply, and the investigator's task has been to interrupt the viruses's activities without throwing a spanner into the cells' essential workings. Many antimetabolites—particularly benzimidazole derivatives—have been tested as antiviral agents,[25] but they either have not restrained the viruses or have done so only at doses which have proved too toxic. Now TAMM reports that the hydroxybenzyl derivative of benzimidazole (H.B.B.) has distinct antiviral activity which is limited to poliomyelitis, Coxsackie, and ECHO viruses. H.B.B. protects cells in the test-tube against damage by these viruses, and it also has some protective action in experimental infections in animals. Especially noteworthy is the fact that its antiviral action is restricted to three enteroviruses; there is hope here of finding selective sites for viral inhibition with the accurate aim of a rifle, in contrast to the blunderbuss effect of antimetabolites which hit everything at once. Similar specificity in antiviral action is a feature of N-ethylisatin β-thiosemicarbazone, which was found by BAUER and SADLER [26] to protect mice from infection with alastrim virus, but is apparently inactive against some other pox viruses or against unrelated viruses.

A second antiviral substance is helenine,[27] a nucleoprotein elaborated by the mould *Penicillium funiculosum*. Helenine also shows specificity in its antiviral spectrum, and it has some protective action in animals infected experimentally with influenza and encephalomyocarditis viruses. SHOPE [28] found that helenine acted synergistically with small amounts of immune serum; in doses which separately did not protect significantly, these substances together protected 50% of mice against the lethal action of encephalomyocarditis virus.

The third substance discussed by TAMM is interferon, which has been described in a series of publications by ISAACS and his colleagues at the National Institute for Medical Research. Interferon differs from the other antiviral substances in being produced naturally by cells in response to virus infections.[29] It therefore has some of the characteristics of an early immunological response to virus infections, rendering cells resistant to virus multiplication. Thus it acts selectively, inhibiting virus growth without damaging the host cells; but its antiviral spectrum is extremely broad, embracing enteroviruses and influenza, encephalitis, pox, and other viruses. Administered to man it may be thought to heighten a natural mechanism of resisting virus infections, after the fashion of specific antibody [30] or γ-globulin, except that antibody gives specific protection by combining with the virus particles, whereas interferon gives broad protection by increasing cellular resistance to virus multiplication. The main obstacle to the use of interferon as an antiviral agent is the difficulty of manufacturing large quantities by a biological process. But if this difficulty can be overcome, and if interferon behaves in man as it does in laboratory animals, doctors will in a few years be able to face the winter surgeries with more cheer than they can muster today.

20. Kenny, S. *ibid.* p. 1113.
21. Jordon, E. C., Slocum, H. C., Nahas, G. G. *Anesthesiology*, 1960, **21**, 205.
22. Brinkman, G. L., Remp, D. G., Coates, E. O., Jr., Priest, E. M. *Amer. J. med. Sci.* 1960, **239**, 341.
23. See *Lancet*, 1960, ii, 1338.
24. Tamm, I. Lecture at North Carolina Memorial Hospital, Dec. 10, 1960. Reported in *News from the Rockefeller Institute*, December, 1960.
25. Tamm, I. *in* 8th Symposium of Society for General Microbiology; p. 178. London, 1958.
26. Bauer, D. J., Sadler, S. G. *Lancet*, 1960, i, 1110.
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28. Shope, R. E. *J. exp. Med.* 1953, **97**, 601.
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30. Hitchcock, G., Isaacs, A. *Brit. med. J.* 1960, ii, 1268.

Annotations

ORIGINS OF CRIME

STUDIES on the causation of crime have been largely rather unsatisfactory [1]; and a new book by McCord and McCord [2] throws welcome light on this subject, where prejudices and opinions have outnumbered facts. Their assessment of the Cambridge-Somerville youth study, started in the U.S.A. in 1937 by Dr. Richard Cabot to investigate the benefits of counselling delinquents, confirms Powers and Witmer's earlier finding [3] that the boys in this study became no less delinquent than a carefully matched control group. The discouragement in this conclusion is only slightly lessened by the observation that, owing to counsellor turnover and heavy caseloads, the counselling fell far short of Cabot's ideal of close relationship between boy and counsellor. The very extensive original case-records (each containing reports by several counsellors, social workers, and teachers, and at least one psychologist, one doctor, and one nurse, plus those by many community officials who had known the child) provided data collected on many boys before they became delinquent, so presenting a golden opportunity for a longitudinal study avoiding the biases associated with retrospective analysis. Each case was rated on defined categories of personality, and social and family characteristics were assessed by five workers who were unaware of the boy's subsequent career (thus avoiding "criterion contamination"). Reliability was high, three judges obtaining some 80% agreement on a 10% sample. The outcome was based solely on conviction in the Massachusetts and Federal courts—a criterion which, though restricted and open to some bias, has the merit of objectivity.

Intelligence was found, as in other studies,[4] not to have much relation to the development of delinquency, nor was physical illness of much importance. Social factors were also not strongly related to criminality: "Undeniably a slum neighbourhood can mould a child's personality—but apparently only if other factors in his background make him susceptible to the subculture that surrounds him." This might seem to clash with the concept of areas with a tradition of delinquency as a norm, developed by Clifford Shaw in Chicago and described by Mays [5] in Liverpool. But Mays states: "In certain areas with a tradition for antisocial behaviour, children tend to react to personal difficulties or to strained relationships in the home by delinquent activity"—a conclusion that agrees with the McCords'. Although this has not always been the case,[6 7] it now seems that there is little relationship between delinquency and social class.[8] Mays observes, however, that, whereas violence and rowdyism of public-school boys is tolerated, there is no such consent for street gangs; and the McCords found that children who lived in "good neighbourhoods", even though they came from neglectful families, tended to channel their frustrations in a non-criminal way. Stott's finding [9] that there is a very high correlation between delinquency and maladjustment in other spheres suggests that, even in delinquency areas, criminal behaviour is not usually "normal".

Confirming the previous work of Glueck and Glueck,[10] the McCords found that the home background was of predominant importance, with cohesive homes producing few criminals and quarrelsome and neglectful homes many. "Broken" homes were less important, and clearly their influence has been overstressed. Comparing homes "accidentally" broken by death and those disrupted by separation or divorce, Bannister and Ravden [11] showed that the latter were more conducive to delinquency. A broken home may be a crude reflection of parental instability, and possibly it is often worse that a child remain in a home made dysharmonious by quarrels and lack of affection than that the home be broken.[12] The effect of discipline proved complex in that the method used—punitive or love-orientated—was not important; but lax or erratically punitive discipline was related to criminality, although the harmful effect was largely dissipated if the home was otherwise sound.

Of all the influences studied the mother's personality seemed to be the most significant in the genesis of criminality. Maternal passivity, cruelty, neglect, and absence were all associated with a high degree of all types of criminality. On the other hand, maternal love, even if complicated by an overprotective attitude, by anxiety, or by neurosis, was generally associated with low rates of crime. In keeping with a study in this country,[13] the father's personality was also found to be of great importance; and paternal absence, cruelty, or neglect tended to produce criminality in a majority of boys.

This work is clearly important, although some caution must be exercised in applying to other populations results from an area where 40% of the boys became delinquent. The McCords were interested in the prediction of delinquency; and the Gluecks' latest work [14] summarises accomplishments so far in this direction. By comparison of delinquent with non-delinquent groups they isolated the relatively few crucial factors which distinguished the one from the other, producing a weighted score which gave a predictive value for the development of delinquency in any individual. The factors were very similar to those of the McCords, and in fact the application of their prediction table to a sample of 100 boys in the Cambridge-Somerville study produced a 91% accurate forecast.[15] But, as in most other studies, this was an "after-the-fact" prediction, and validity can really be tested only by a prospective study. Glueck [16] reports such a study, prediction having been made on 223 6-year-olds in New York city—a group of different race and age from that used in constructing the table, and so a rigid test of it. The children are still only 13 years of age and the follow-up is unfinished, but hitherto some 95% of the predictions for non-delinquency and 45% for delinquency have been borne out. Tables have been constructed to forecast outcome at different stages in the

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14. Predicting Delinquency and Crime. By SHELDON and ELEANOR GLUECK. Cambridge, Mass.: Harvard University Press. London: Oxford University Press. 1960. Pp. 283. 52*s*.
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16. Glueck, S. *ibid.* 1960, **51**, 283.

delinquent's career with different forms of management. Factors are not always quite the same; but "first and foremost is the permeative influence of certain elements in the family life". Residence in a delinquency area is not of much predictive value, but behaviour at school and the age of onset of antisocial behaviour are important at most stages. Surprisingly perhaps, offenders from poorer homes turned out better risks under various forms of penocorrectional treatment than did those from more comfortable homes.

Much remains to be done in testing the validity of these scales; but the results so far are promising and the scales should prove of value to the courts. The scales cannot be immediately applied to the different situation in England; but the sooner a similar approach is tried here the better, and Mannheim and Wilkins [17] have made a start in connection with borstal training. The Gluecks explicitly affirm that they do not wish to make jurisprudence mechanical—it is for the judge to form a workable programme that takes into account legal demands and social limitations as well as clinical findings. Nevertheless "the predictive approach opens up a promising path through the dense forest of guesswork, hunch, and vague speculation concerning theories of criminal behaviour. It gives hope of the ultimate transformation of criminology into a discipline approaching scientific stature".

INFECTION FROM POULTRY

NO-ONE is sure who was responsible for the original observation that young animals of many kinds grow more quickly if given small daily doses of an antibiotic, but to enrich feeding-stuffs in this way is now accepted agricultural practice. The risks to man in this process are few and, such as they are, derive from the habit of most bacteria of developing strains resistant to an antibiotic if bred for any length of time in a medium which contains sublethal amounts of that antibiotic. Such methods can apparently increase the proportion of poultry-keepers who harbour penicillin-resistant staphylococci on their persons, but whether this matters much is open to argument.[18]

Now we have news of what may be a more dangerous development.[19] Another use of antibiotics has been to defer the decay of meat and fish without impairing taste. The gain in "life" is not astronomical, but is enough to make marketing easier and more profitable. The method under examination [19] consisted in immersing the carcasses of poultry in slush ice containing 10 p.p.m. chlortetracycline for 2 hours, which inhibited the growth not only of the bacteria which commonly cause spoilage but of staphylococci and salmonellæ. Infection with *Salmonella typhi-murium* is not unknown in apparently healthy chickens, and this treatment might seem an added safeguard to the customer's health. Chlortetracycline is, however, used quite frequently as a growth-promoting agent in chicken foods, and there is evidence that this practice can give rise to strains of salmonellæ resistant to this antibiotic.[20] Treatment of the carcasses with chlortetracycline will not prevent the growth of these resistant strains, and in fact accelerates their growth in relation to that of the spoilage organisms if the carcass is held at room temperature. If the bird is not cooked thoroughly someone is going to get the merry-go-whimbles.

We would not wish to exaggerate this danger. Many antibiotics increase the rate of growth of young animals: any broad-spectrum antibiotic will probably inhibit the spoilage organisms. What matters is that the same substance shall not be used for both purposes. It may be significant that in the U.S.A. poultry cause food-poisoning more often than they do here, and that the use of antibiotics for rearing and for preserving has been the custom for a longer time than here. But the crux of the matter would seem to be the number of chickens destined for the table which are naturally infected with *S. typhi-murium* and the proportion of these which are resistant to antibiotics. (Other salmonellæ may be equally dangerous but *S. typhi-murium* is the commonest which is pathogenic to man.) If the number of infected birds is large the fact will be obvious to the farmer by reason of a mortality-rate, which will render his rearing unprofitable. If the incidence is 1% or less the number of any test sample must be large if any accurate generalisation is to be made. Gregarious animals such as fowls add another trouble to statistical analysis: if 1 bird in a flock of 1000 is found to be infected, is the whole flock a potential source of infection? To obtain a reasonable estimate of the number of infected birds in this country calls for the examination of at least 100,000 cloacal swabs—and then the result might be correct only for the areas where these were collected. But until this information is to hand we cannot tell whether these chlortetracycline-resistant strains of salmonellæ are a real danger or a bogy.

When the source of infection is eggs quantitative estimation of the danger is even more difficult. If a hen is infected with *S. typhi-murium*, does it pass this infection to 100% or 50% or 1% of the eggs which it lays? An outbreak of enteritis due to *S. typhi-murium* in an institution was attributed with good cause to the consumption of egg-nog by the inmates.[21] Three previous epidemics were probably derived from the same source. The eggs came from a flock of 5050 laying birds. Each of these was bled and the serum examined for O agglutination of *S. typhi-murium*. 94 gave positive reactions. 9 of those with the highest titres were killed, and of these 2 gave evidence of infection with *S. typhi-murium*. 29 others were isolated and produced 1117 eggs of which 3 yielded the same organism. It would need at least a senior wrangler to estimate the number of sources of infection in this flock. It is fairly clear that some of those which gave positive agglutination reactions no longer harboured the organism: experience in this sort of problem suggests that some which gave negative reactions were in fact infected.

What is clear is that, given the right conditions for the multiplication of the bacteria, a very few infected eggs can cause illness in a large number of people who eat egg-nog. In the same way the milk from one cow excreting *S. dublin* incorporated in 500 gallons can contaminate the whole lot if it is held under conditions which encourage bacterial multiplication. Most of us have probably eaten hens' or ducks' eggs containing salmonellæ, but they have been well cooked: the danger lies in an uncooked, nutritious, fluid food prepared in large quantities and insufficiently cooled. The afflicted institution, by the way, now pasteurises its egg-nog.

17. Mannheim, H., Wilkins, L. T. Prediction Methods in Relation to Borstal Training. H.M. Stationery Office, 1955.
18. See *Lancet*, 1960, i, 1338.
19. Hobbs, B. C., Reeves, J. C., Garside, J. S., Gordon, R. F., Barnes, E. M., Shrimpton, D. H., Anderson, E. S. *Mon. Bull. Minist. Hlth Lab. Serv.* 1960, **19**, 178.
20. Gordon, R. F., Garside, J. S., Tucker, J. F. *Int. vet. Congr.* 1959, **2**, 347.
21. Philbrook, F. R., MacCready, R. A., van Roekel, H., Anderson, E. S., Smyser, C. F., Sanen, F. J., Groton, W. M. *New Engl. J. Med.* 1960, **263**, 713.

INFECTION OF INTERVERTEBRAL DISCS

REVIEWING 10 cases of infective lesions of intervertebral discs, Scherbel and Gardner [1] found that in 5 the infection had been preceded by diagnostic or therapeutic procedures on the spine. Puncture of a disc may be followed by backache with sciatica; and Gardner et al.[2] suggested that this pain was nearly always due to infection rather than to mechanical damage. Infection after laminectomy with removal of a disc was reported by Sullivan et al.[3] The possibility of venous spread of infection in the absence of direct disc injury was revealed by Batson's [4] study of the communication between the pelvic and vertebral venous systems. Of Scherbel and Gardner's 10 patients 6 had infection of the urinary tract.

While the clinical course of these lesions varies, severe pain with a rigid back is a common clinical feature. The temperature is usually raised, and the erythrocyte-sedimentation rate increased. Radiographic changes may be absent for some weeks, and when present may consist only in narrowing of the disc space followed by vertebral-body destruction. Bony fusion between adjacent vertebræ is a common late sequel.

Where the infection is detected at an early stage chemotherapy and immobilisation may suffice. Where destruction is greater the disc space may need curettage, and a posterior abscess makes operation imperative. Perhaps the most difficult cases are those in which the infection is of low grade and the symptoms may be wrongly ascribed to an exacerbation of the condition initially demanding treatment. It seems quite clear that many of these lesions are missed, at least in the early stages, and that in time some resolve spontaneously.

TUBERCULOUS PERITONITIS AND ALCOHOLIC CIRRHOSIS

IT is difficult to ascertain how often tuberculous peritonitis complicates the later stages of cirrhosis of the liver. Rolleston and McNee,[5] reviewing European reports up to the end of last century, suggested that tuberculous peritonitis occurred in as many as 9% of cases of hepatic cirrhosis; but in 1942 Ratnoff and Patek,[6] in a study of patients with cirrhosis in several New York hospitals, found a lower incidence which mirrored the general decline in tuberculosis and particularly in abdominal tuberculosis. Certainly in the non-alcoholic cirrhotics seen now in Britain, tuberculous peritonitis is uncommon. But from an adult medical unit of the Boston City Hospital comes a report that, notwithstanding a general decline in extrapulmonary tuberculosis, tuberculous peritonitis is being encountered as frequently as twenty-five years ago. About 40% of these patients with tuberculous peritonitis have alcoholic cirrhosis.

What is most striking in this report by Burack and Hollister [7] is that tuberculous peritonitis remained unsuspected during life in 55% of the cirrhotics but in only 15% of the patients who did not have cirrhosis. In the cirrhotic group tuberculous peritonitis was firmly diagnosed during life in only 6 out of 30 patients. The difficulties, therefore, of establishing a diagnosis of tuberculous peritonitis in the absence of conclusive evidence of tuberculosis elsewhere seem to be much increased when the patient also has cirrhosis of the liver. This led Burack and Hollister to compare retrospectively the findings in a group of cases with simple ascites secondary to cirrhosis of the liver and in a group with both cirrhosis and tuberculous peritonitis.

No clear-cut distinguishing features emerged from an analysis of the clinical manifestations and of the characteristics of the ascitic fluid. Abdominal pain, abdominal tenderness elsewhere than over the liver, and fever are uncommon in uncomplicated cirrhosis and should arouse the suspicion of coexisting disease, of which tuberculous peritonitis is only one possibility. Clinical hygrometry of ascitic fluid is inaccurate without correction for temperature, and no single value demarcates a transudate from an exudate. When the total protein exceeds 2·5 g. per 100 ml. of the fluid, or when the leucocytes exceed 250 per c.mm., tuberculous peritonitis is a distinct possibility, especially if the proportion of polymorphs does not exceed 20% of the total leucocyte-count. In this series tubercle bacilli were never demonstrated microscopically. One in three of the tuberculous fluids inoculated into guineapigs proved to be bacteriologically negative, and over half the cultures for tuberculosis were negative; but considerable overlap justifies the use of both methods in diagnosis. In some patients in this series the diagnosis was established only on exploratory laparotomy; the value of the less severe operation of peritoneoscopy was not assessed.

NEW YEAR HONOURS

THE medical knighthoods in the Honours List are few but notable. Mr. Denis Browne, who is created K.C.V.O., has contributed much to the reputation of Great Ormond Street, especially in the surgery of congenital defects; and we can also be grateful to him for being one of the personalities of our profession—witty, contentious, and real. At the National Institute for Medical Research, of which he is deputy director, Dr. C. H. Andrewes has long been the wise but enterprising head of the famous department of virology, having charge both of the World Influenza Centre and of the investigations on the common cold at Mill Hill and at Salisbury. The unit's recent isolation and propagation of viruses from colds [1] is, we may hope, a step towards control of the common cold itself, while the work on influenza, in which Andrewes was early concerned,[2] should prevent any repetition of the epidemiological disaster of 1918. The third of the new knights is, like Mr. Browne, an Australian by birth and a Sydney graduate; but he too has become very much part of the London scene. Professor of radiology since 1942, Dr. Brian Windeyer is among the foremost in his specialty; but in the past six years he has won new respect as dean of the Middlesex Hospital Medical School during its very interesting new phase of development. The fourth knighthood is conferred on one of the senior physicians in Australia, Dr. Rowden White, who was vice-president of the Royal Australasian College of Physicians from 1943 to 1946 and has been a generous and discerning benefactor of education, the arts, and medicine.

Major-General H. E. KNOTT has been appointed director-general of Army Medical Services in succession to Lieut.-General Sir Alexander Drummond.

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2. Gardner, W. J., et al. *Arch. Surg. Chicago*, 1952, **64**, 355.
3. Sullivan, C. R., Bickel, W. H., Svien, H. J. *J. Amer. med. Ass.* 1958, **166**, 1973.
4. Batson, O. V. *Ann. Surg.* 1940, **112**, 138.
5. Rolleston, H., McNee, J. W. Diseases of the Liver, Gall Bladder and Bile Ducts; p. 252. London, 1929.
6. Ratnoff, O. D., Patek, A. J. *Medicine*, 1942, **21**, 207.
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Points of View

THE OTHER PART OF MEDICINE *

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THE basis of rational therapy is always a theory about the causation of the illness. Unfortunately, theories are anything but permanent, and when they change all therapy based upon them must change too.

When I was a student the patient who was going to have a major operation was given a very light meal, plus a fairly large dose of castor oil, on the previous day, and practically nothing from then until the operation. Certainly no fluids: on the contrary, early in the morning he was given an enema. After the operation he was nursed flat on his back and, so that he should not move or raise his head, fairly heavy sandbags were put at his side and across his abdomen. Today, because of the change in our theories, every item of this regime would be considered a major mistake.

It is understandable, therefore, that doctors have become uneasy about therapeutic techniques based solely on pathological theories: they have had too many unsettling experiences with techniques which seemed to be firmly established yet disappeared into the limbo a few years later. To reassure themselves they had to look for a safer foundation. More and more people think nowadays that this has been found in the double-blind experiment.

Two groups of patients, all suffering from the same illness, are matched for sex, age, and social status. Both groups are treated with pills which look the same and taste the same, but some of the pills contain the therapeutic agent under trial, while the others do not. The experiment is arranged so that neither the patients who take the pills nor the doctors who give them and observe the results have any knowledge whether the pills are real or fake. This is known only to a third person who remains completely uninvolved, who if possible does not even see either the patients or the doctors in charge of the treatment, and to whom the observed results are then submitted for final judgment. It is hoped that in this way any proposed therapy can be judged impartially and objectively.

Undoubtedly this method is highly scientific and objective, and its results are reliable. Furthermore, its results are independent of any theory. The only trouble is that its application is painfully limited. In order to be safely controlled, the patient's participation in the experiment must be kept minimal: the only thing he is called on to do is to swallow reliably the pills prescribed and to report any sensation and especially any change of sensation to his doctor. Even the doctor who treats the patient may be limited in his participation. The only person for whom the whole set-up must make sense is the master-mind—the third, uninvolved, doctor.

The double-blind experiment usually presupposes an entirely objective situation in which any doctor may treat any patient with any illness with any sort of therapeutic agent provided their emotional involvement in each other and in the therapy can be kept very slight. But wherever therapy is based essentially on an emotional understanding of the pathogenic processes by the patient, such an experiment is out of the question. To match patients according to age, sex, and social status is sadly insufficient, in view of the many further determining factors such as the occurrence and timing of deprivations in early childhood, the patient's attitude to authority, his sexual maturity, and his ability to obtain regular sexual satisfaction. Moreover, whatever the illness, an obsessionally reliable man will give utterly different results in any psychotherapy from an overexcitable highly strung one. Even all this, however, is only a minor difficulty compared with the impossibility of giving placebos in psychotherapy. It is utterly impossible to give the patient, according to a time-table at a given moment, prearranged interpretations or a certain kind of sympathetic understanding as prescribed by a third uninvolved doctor. And whereas it is easy to persuade a patient to " swallow " a pill, whatever its contents are, one cannot make him " swallow " a piece of understanding or an interpretation which does not make sense to him at that moment.

Evidently we have to do with two different classes of therapy: one can be carried out without much cooperation from the patient, who need not even understand it or accept its implications, while the other class can be effective only if the patient's individual history, his character, his present complaints and his whole illness on the one hand, and the therapy offered to him by his doctor on the other hand, can make sense together. Roughly the same holds true for the doctor. During the therapeutic work belonging to the first class there is no need for him to identify himself with his patient; but if he undertakes therapeutic work belonging to the other class, he cannot avoid becoming involved in the therapeutic relationship. True, he must be able to control his involvement, but it is only by that involvement that he will " understand " the illness and be able to offer meaningful help to his patient.

Although this classification sounds very sensible and pedestrian, it is in fact revolutionary, as it will become clear if we examine some of its repercussions.

* * *

To create a safe basis for our discussion, let me mention first the history of a woman who was later found to have refused sexual intercourse for at least two years and had possibly had a very unsatisfactory regime much longer. During this time of abstinence she developed three diseases which were apparently independent of one another and which were diagnosed as (1) probable peptic ulcer, (2) spastic colon, and (3) the clicking-rib syndrome. Looking at them together we cannot exclude the suspicion that they might be secondary consequences only of an underlying general cause. Moreover, the husband's periodic drunkenness might be considered as a fourth illness stemming from the same general cause. In this story we can find yet another example of the patient with an insoluble problem who comes to his doctor with various " offers " to which it is the doctor's task to respond with a proper diagnosis.

Doctors brought up in the spirit of the double-blind experiment will be inclined to take the various " offers " at their face value; and in so doing they will feel that they are acting as proper scientists, in the way they were taught in their teaching hospitals. But the situation becomes more difficult and perhaps less exact if for some reason they decide to go " deeper ". Whereas any properly trained doctor who is familiar with the present

* From a contribution to the symposium on Psychotherapy by the General Practitioner, at the annual meeting of the Deutsche Gesellschaft für Psychotherapie und Tiefenpsychologie, held at Wiesbaden in April, 1960.

state of medical knowledge can prescribe for an uncertain peptic ulcer, a spastic colon, and perhaps even a clicking rib, and certainly can be instructed by a third especially well-trained doctor what to prescribe for any of these conditions, the situation is utterly different for the kind of treatment—the kind of psychotherapy—that has to be discovered jointly by the patient and his doctor, for his particular case. To be efficient this therapy must make sense to the patient and to the doctor at the same time.

In some cases—particularly when the patient presents or " offers " several illnesses, his family doctor has a much better chance to get hold of and to understand the real problem than any specialist. To prove that specialists are not necessarily more successful doctors, we asked one of the members of our seminar to pick out one of his patients who had had many hospital and specialist examinations and treatment and offer him a proper psychological examination lasting about an hour.

The patient chosen was Mr. B, aged 53, with a long history of duodenal ulcer and other physical ailments. In the $6^1/_2$ years after joining the practice Mr. B had been away from work for a total of over 400 days, and had been in hospital five times for a total of 12 weeks: his file contained 34 reports from specialists. Every specialist who saw him had diagnosed properly that he was a neurotic man but had then gone on treating his array of serious and verifiable illnesses. This was the patient that our somewhat doubting doctor selected for testing our ideas. Out of the blue he rang him up and asked him to come for a long interview.

Mr. B's remarks were bitter, devastating, and uncontradictable; but the doctor learned that Mr. B started his working life as a clerk but did not like his job and changed it to become a private chauffeur for twenty years. He was quite healthy till his employer retired and as a parting gift procured him his present job where Mr. B works as an anonymous clerk in a large office. By the end of the hour, doctor and patient had reached an understanding that in future they could relate his ill health to his feelings about his work and the rest of the world. Soon afterwards the orthopædic surgeon who was looking after a crush fracture of Mr. B's first lumbar vertebra decided that he needed hospital treatment and whisked him away; but in due course he was discharged from hospital and resumed his regular attendance in the surgery to collect his prescriptions for antacids and sedatives. What was different was that he no longer pestered his doctor with complaints, did not lose one day off work for illness in a year, and asked for no night calls. Imperceptibly—nobody knows when—he ceased to be called in the practice " that man B ".

A year after the first interview Mr. B reported that recently his stomach pains had become worse. When the doctor asked whether anything in his life had become more difficult, he began by denying any knowledge of such a change, but after some hesitation and puzzlement he added that it might be connected with the impending change in his office to automation; the office will be still more impersonal than now. Over the past few weeks they had had experts studying everybody's job in order to devise the new machines. The puzzlement disappeared from Mr. B's face, he collected his prescriptions and departed.

Only when the doctor heard this story discussed in the seminar did he realise that apparently what mattered most to Mr. B was to be in personal relationship to someone (like his former employer) who appreciated his work. Mr. B started his illnesses as soon as the personal relationship had to be terminated and he became an impersonal clerk. If this explanation is correct and what Mr. B needs for his health is appreciation of his work and efforts, then the telephone call out of the blue was a powerful therapeutic agent. He responded to it, indeed, at a stage when the doctor himself remained in the dark; but the doctor is to be congratulated on giving him (though not quite intentionally) a chance to unburden himself when he felt threatened by the automation and reported an increase in symptoms.

This kind of diagnosis, and of course the treatment based on it, is very far from being precise or rigorous. It certainly cannot compare in this respect with any of the findings of the many specialists who treated Mr. B. In reaching the conclusion that in future they would relate Mr. B's ill health to his feelings about his present work and the world around him, neither doctor nor patient felt it necessary to distinguish carefully between so-called organic and functional illnesses: they talked merely of ill health. Many people will feel this an unforgivable, rash, and dangerous generalisation, perhaps even a retrograde step unworthy of a scientifically trained doctor. Still, this highly imprecise formulation and the treatment that it represented worked better than all the rigorous and precise diagnostic formulations and the treatments based upon them, contained in the 34 letters written by specialists and preserved in Mr. B's file. Further, when early this year Mr. B complained of exacerbated stomach pains, the doctor did not send him for gastroscopy or barium meal, which would be unavoidable steps towards a diagnosis in rigorousness and precision, but asked him whether he had experienced any new difficulties in his life. This enabled Mr. B to realise—one step ahead of his doctor—that he feared that even the little personal relationship that remained to him would be taken away by the automation; rather a tentative and not at all precise formulation again.

* * *

One part of medicine—what we may call hospital or scientific medicine—maintains that any progress must be towards more rigorous and more precise diagnosis and towards a rational therapy based on this. They can marshal very powerful arguments for their claim; for medicine has indeed developed in a magnificent way under the influence of this scientific spirit. But perhaps we are allowed to ask what the price has been that all of us, doctors and patients alike, have had to pay for it.

One of the answers has been given on many occasions: the price has been the parcelling out of medicine, and with it the patient, among the ever-increasing number of specialists. Admittedly each of them does his job very well indeed; the trouble is that all of them tend to close their files as soon as the patient has moved over to another of the little fenced plots called specialties. Mr. B had collected 34 reports of specialists and was still ill, although I have no doubt that the surgeon who operated on his anal fissure, and the orthopædist in charge of his crushed vertebra, have closed his case as finally dealt with, possibly even as successfully treated.

The other great shortcoming of scientific or hospital medicine is the restricted nature of any follow-up. As a rule, hospital and patient are in contact for only a few weeks to a few months, and the specialist is interested only in a restricted field. If our first patient with her duodenal ulcer and her chest pain had been referred to a gastroenterologist or a lung specialist, it is highly unlikely that either of them would have asked whether her husband was an occasional drinker or whether the couple had a proper sexual regime. The demand for precision and rigorousness apparently involves a restriction of the field under observation, and it is here that hospital medicine shows its greatest difference from the work of the general

practitioner, who simply cannot restrict his observation in this way. The family doctor has to look after the family whatever their need or complaints may be; and, since he sees them anyway, he does not have to write letters and implore his patients to come for a check-up. Yet in the present medical atmosphere, because the practitioner's routine does not allow him to be as precise and rigorous as the hospital scientists are and as he was taught to be, he truly feels himself inferior to his colleagues in the hospitals. A further price which we are paying for the great achievements of scientific, precise, medicine is the acceptance of general practice as something second-rate compared with the proper medicine practised in hospitals.

This, however, is not all. There is a third, a very high price, to be paid as well, and that is the giving up of the idea of the illness as a meaningful stage in the development of the individual and the degrading of any psychotherapy to a not quite proper role. Illness is generally conceived nowadays as a kind of accident falling upon a human being —an accident with which he had no connection previously. Of course there are illnesses known to arise from congenital states and others in which the importance of the pre-morbid personality is fully acknowledged. I readily admit that there are many transitional states which make a clear distinction very difficult. Still, I would like to contrast the idea of an illness as an accident with another idea according to which illness is due to a lack of integration brought about by some disturbance in the relation between the individual and his environment. This would mean that illness or "ill health" must be considered as a meaningful phase in a person's life history, and one of the tasks of rational therapy would be to help the patient to achieve the integration which he could not achieve on his own.

The more an illness resembles an accident, the better are the results of hospital medicine; and it is here that the double-blind experiment has its proper application. On the other hand, the more an illness is due to a lack of integration the less effective will be the so-called scientific treatments and the less applicable will be the double-blind experiment.

Of course, as just mentioned, a number of illnesses are transitions between these two extremes, thus they constitute a borderland with inexact boundaries and unsettled proprietary rights—that is, a most important field for research. Fervent lip-service is paid to the urgency of this research, foremost in the United States, under the slogan of *comprehensive medicine:*

> Unfortunately in most hospitals this comprehensive medicine means merely the enlisting of the services of a few more specialists—among them sociologists, social workers, and nurses. In theory, all the various specialists concerned with one family discuss together the whole field of problems; but in these joint conferences some of the specialists are represented mainly by paper reports. A further puzzling fact is that, though the investigation and diagnosis is done under this comprehensive banner, the treatment is not. This is delegated, as is customary in every teaching hospital, either to the most junior member of the staff or to a student; and, since students and junior members change very rapidly, when the patient or another member of his family turns up a few months later for a second piece of advice or a follow-up he will meet probably the same social worker or the same nurse, and will certainly have the same file, but hardly ever the same doctor who treated him the last time.

If I say that scientific or hospital medicine works on the principle that any doctor with the same training can treat the same patient equally well, I expect to provoke some resistance. Hospital scientists will argue that the head of the service, and possibly his first assistant, remain the same and will see to it that their junior staff will do their job properly and sympathetically. But even if we agree that they succeed in this, there cannot be any doubt that the quality of the junior staff varies somewhat from one person to another, and that their personality and character are never the same as their predecessors. However hard the senior staff try to maintain a uniform service this service can never be uniform, unless it is so standardised as to become inhuman.

To get over this, the whole structure of the teaching hospital—the real home of scientific medicine—would have to be changed, which I think is unrealistic to ask. What then is the solution? My proposition is that we ought to recognise the existence of these two kinds of medicine—(1) scientific or hospital medicine, as it is taught and practised in pure form at the teaching hospitals, and in a more or less impure form in other hospitals with fewer resources, and (2) the other kind of medicine which might be called medical practice.

The aim of scientific medicine should remain as it is now—a diagnosis in rigorousness and precision, a rational therapy based on this sort of diagnosis and validated under as strict conditions as possible on the model of the double-blind experiment. For some time to come this medicine will be the science of specialists, who possibly will have only a limited contact with their patients and will be able to observe only a limited field—i.e., their specialty. The other medicine, which I call medical practice, will have to forgo the ambition to become as exact as her sister. Her ambition will be not so much diagnosis in precision as diagnosis in depth; and it will be many years, possibly generations, before doctors can refine their findings and their language for describing them so that it will match the achievement of scientific medicine. As their diagnosis will not be precise, objective, or scientific, the treatment based on it will not lend itself to a validation according to the model of the double-blind experiment. They will have to develop new criteria, a different kind of scientific objectivity, which may be called *whole-person pathology or whole-person medicine*, in which the main task will be to *understand the meaning for the person of the complaints and illnesses that he offers to his doctor*. The aim of therapy will then be to *enable the patient to understand himself*, find a better solution for the problem facing him, and thus achieve the integration which has not developed or has broken down because of disturbed relationship of the individual with his environment. This is the place of psychotherapy in medicine.

Looking at the situation thus, we may say that there is no need for controversy or competition between the two medicines. What must be done, however, and must be done from both sides, is to find out what sort of conditions can be treated by what kind of methods; and it is here that great difficulties have to be expected. The tacit conclusion that hospital teachers and methods are far superior to anything else will have to be revised. In many conditions it is true, but in others the patient can get more help from general practice—i.e., from proper psychotherapy. While the methods of hospital medicine are generally more successful in dramatic or critical conditions involving life or death, general practice and psychotherapy may be more effective in securing or maintaining contentment and human happiness—which is perhaps equally important. In modest terms, we may state their aim as to free people from unnecessary miseries in everyday life.

Special Articles

FOREIGN DOCTORS IN THE U.S.A.

FROM A CORRESPONDENT

THE United States attracts many doctors of other lands for a variety of reasons, including the present high prestige of American medicine, the high standard of living, and the opportunities for research. Some doctors go to spend a year or so there " to see what it is like " before they settle down in their own country; others, disgruntled with the medical set-up at home, emigrate to what they regard as the land of the free doctor. Conversely, American hospitals welcome foreign physicians—some to promote international bonhomie, some to provide specialist training for those from places where it cannot be got, and a great number to fill the otherwise unfillable vacancies in their house staff. The State Department's Educational Exchange Program, by provision of special visas, made it easier for foreign doctors to train in the United States, and the number has grown till last year a survey showed that there were no fewer than 8392 foreign-qualified doctors training in 40 States (some States will not allow foreign graduates to practise at all).

The foreign doctors play a large part in staffing the hospitals: last year in Massachusetts, for instance, 36% of the interns and 28% of the residents were graduates of foreign schools—and 6% of the internships and 6% of the residencies were unfilled.[1] As might be expected, the proportion of the house-officers who qualified abroad tends to be higher away from the teaching centres, and in Massachusetts it ranges from 6·5% at the Massachusetts General Hospital to 100% in many of the smaller hospitals on the outskirts of Boston and elsewhere in the State.

This situation is bound to lead to many disappointments. Some of the foreign doctors have found that the postgraduate training they have received has been of poor quality, and there has been a regrettable tendency for some hospitals to use the foreign graduates (not to mention some American graduates) as cheap labour. On the other hand, many hospitals have found the foreign doctors to have standards lower than those customary in the United States; and there have been difficulties over language, many doctors arriving in the United States unable to understand English. (Some hospitals have actually set up special intensive training programmes to teach their housemen English before letting them loose on the patients.) Some lay magazines, eager for any stick to beat the medical profession and the hospitals with, have published alarming articles about the poor quality and linguistic difficulties of some foreign graduates.

A SPECIAL EXAMINATION

Deciding that something had to be done, and that it was impossible to assess adequately every medical school in the world, the American Medical Association, the American Hospital Association, the Association of American Medical Colleges, and the Federation of State Medical Boards together sponsored the Educational Council for Foreign Medical Graduates. Established in 1957, this body examines credentials of foreign graduates, and twice yearly it holds an examination for them, at centres throughout the United States and throughout the world.[2]

This is a multiple-choice examination (in which some 90% of the questions are on clinical subjects and the rest on basic sciences), and an English test, in which a history is dictated and the candidate is required to write it down as it would appear in the case-record. The pass-mark is 75%, and those who score 70–74% are given a temporary certificate, valid for two years.

Many hospitals require foreign graduates (the term includes United States citizens if they went to medical school abroad) to have the E.C.F.M.G. certificate before they can be accepted. Moreover, some 25 States insist on the certificate before they will consider an application for a State licence to practise, and some specialty boards require foreign graduates to have the certificate before admitting them to the specialist examination. But many hospitals, fearful of being unable to fill their house-appointments (the pass-rate was less than half in the first four examinations) have made no such stipulation.

SANCTIONS AND THEIR EFFECT

Eventually the American Hospital Association decided to withdraw its accreditation from hospitals employing foreign graduates not licensed by the E.C.F.M.G.; that is to say, their internship and residency programmes would no longer be officially approved. This applied to those already in training as well as to those not yet appointed. A deadline was set, and as a result 6029 candidates sat the examination in last March (when 33% passed) and 8713 sat it in September (when 43% passed and 28% were awarded a two-year extension).

Those who failed the examination include nearly 2500 doctors now in the United States,[3] and their situation has created many problems—for the doctors themselves, for the hospitals employing them, and even for the State Department. The hospitals have the choice of dismissing them (often without the possibility of replacing them, and often in breach of a contract in the case of those appointed, before the deadline was set, for a programme lasting several years), or of retaining them, with the risk of being denied accreditation, which would damage the hospitals' prestige and make it impossible ever to attract house doctors of high quality.

Many hospitals, believing that the situation is hopeless without uncertified foreign graduates, will defy the ban and risk losing their accreditation and lowering their standards of work. Some hospitals, feeling an obligation to their uncertified housemen, are considering plans to employ them in non-clinical positions[4]—not a very satisfactory solution, for they will still need people in the clinical appointments, and they may run into financial difficulties if they duplicate their staff, while the doctors concerned, though still employed, will not be getting the training and experience they sought.

Many of these doctors are on temporary visas, valid only while they are taking specific training; and the State Department is concerned about the adverse effects on foreign relations of the mass deportation that is threatened.

Finally, the foreign doctors themselves are not only unhappy at having their careers interrupted; many feel bitter about the examination, claiming that it is unfair.[5] Certainly, it is not the same examination that American graduates take (the great majority sit the examination of the National Board of Medical Examiners, which cannot give its certificate to foreign graduates; those who pass

1. Bearse, C. *New Engl. J. Med.* 1960, **262**, 1014.
2. Those who wish to do postgraduate clinical work in the United States must generally take the examination before appointment; the address is Educational Council for Foreign Medical Graduates, 1710, Orrington Avenue, Evanston, Illinois, U.S.A.
3. *New York Times*, Nov. 19, 1960.
4. *Daily Item*, Port Chester, N.Y., Nov. 23, 1960.
5. *Resident Physician*, 1960, **6**, 67.

can easily obtain a licence in 44 of the 50 States); and its multiple-choice style is unfamiliar to those used to essay and oral examinations. But your correspondent, who has sat both the E.C.F.M.G. examination and part 2 (the clinical subjects) of the National Board examination, found the E.C.F.M.G. test much easier. Poor knowledge of English would be a handicap in the examination—as it would in clinical practice (though in some parts of the United States a knowledge of Finnish or Ukrainian would be more useful to the doctor than a knowledge of English). A more valid criticism might be the unfairness of preventing people in the middle of their training from completing it because they fail a test that had not been devised at the start of their training; and it is hard to see the necessity for a new examination when the National Board is well established and will examine foreign graduates for a specific purpose (e.g., as a screening process before they can be examined for a Massachusetts State licence).

A BRITISH PARALLEL?

In Britain, where it is becoming harder for small hospitals to find housemen and registrars, and many foreign doctors come for postgraduate training, a similar set of problems may well arise; and the authorities might ponder the American experience and ask what lessons it holds for Britain.

GENERAL-PRACTITIONER MATERNITY SERVICES

NEW terms of service for practitioners providing maternity services have been announced by the Ministry of Health.[1] They became operative on Jan. 1.

The initial examination, attendance at an emergency, or during labour at the midwife's request, and a postnatal examination of the mother not later than twelve, and preferably at about six, weeks after delivery are retained. In addition the practitioner will be expected in future to carry out not less than 5 antenatal examinations at intervals, 1 of these between the 32nd and 34th weeks, and 1 at the 36th week of pregnancy; to attend at some stage of labour, either before or at delivery, or as soon afterwards as possible; to visit not less than 5 times during the two weeks after confinement; and, if he is not the patient's usual practitioner, to issue the necessary certificates.

A new applicant for inclusion on the obstetric list will have to satisfy *one* of the following conditions:

(*a*) That he has held a six-month resident appointment in a hospital obstetric unit within the preceding ten years.

(*b*) If such a post has been held, but not within ten years, that he has attended at least a one-week refresher course, or held a two-week resident appointment, supervised by a consultant, in an obstetric unit in the past five years.

(*c*) That he has been in obstetric practice and attended not less than 100 cases in the past five years, being responsible for the antenatal care of all, and having supervised labour and the puerperium in at least 50.

(*d*) That he is on another obstetric list and qualified to remain on it.

(*e*) That within the past two years he has obtained experience as a non-resident in an obstetric unit. The minimum experience in six months should comprise 20 normal deliveries and attendance at 10 abnormal confinements, and at 10 antenatal and 2 postnatal clinics.

After five years the experience of doctors on the obstetric list will be reviewed: to remain on it they will have either to fulfil one of the above criteria or to have attended antenatally at least 50 maternity cases in the five years, and the labour and puerperium of 25.

1. E.C.L. 81/60.

NEW YEAR HONOURS

THE list of honours published on Dec. 31 contains the names of the following members of the medical profession.

K.C.V.O.

DENIS JOHN BROWNE, M.B. Sydney, F.R.C.S.

Knights Bachelor

CHRISTOPHER HOWARD ANDREWES, M.D. Lond., F.R.C.P., F.R.S.
Deputy director, National Institute for Medical Research, London.

ALFRED EDWARD ROWDEN WHITE, C.M.G., M.D. Melb., F.R.A.C.P.
Consultant physician, St. Vincent's Hospital and Children's Hospital, Melbourne; for philanthropic services to the advancement of culture and the development of medical research.

BRIAN WELLINGHAM WINDEYER, M.B. Sydney, F.R.C.S., F.F.R.
Professor of radiology, University of London; dean, Middlesex Hospital Medical School.

C.B. (Military)

Air Vice-Marshal GLEN ALBYN MARTIN KNIGHT, C.B.E., M.B. Melb., Q.H.S.

Major-General HAROLD EDWIN KNOTT, O.B.E., M.D. Dubl., Q.H.P.

Surgeon Rear-Admiral WILLIAM PERCIVAL EDWIN MCINTYRE, M.D. Dubl., Q.H.P.

Surgeon Rear-Admiral GEORGE PHILLIPS, M.B. Edin., Q.H.S.

C.M.G.

LESLIE CECIL LLOYD AVERILL, M.C., M.D. Edin., F.R.C.S.E., F.R.C.O.G.
Medical officer, St. Helen's Maternity Hospital, Christchurch.

SYDNEY SUNDERLAND, M.D., D.SC. Melb., F.R.A.C.S., F.R.A.C.P.
Professor of anatomy, University of Melbourne; chairman, National Radiation Advisory Committee.

C.V.O.

JAMES CECIL HOGG, B.CHIR. Cantab., F.R.C.S.

C.B.E. (Military)

Group-Captain CLIFFORD COCKCROFT BARKER, A.F.C., M.B. Edin., R.A.F.

Brigadier FRANK LEO HUTTER, E.D., M.B. N.Z., F.R.C.S., R.N.Z.A.M.C. (T.F.).

Brigadier ARTHUR PHILIP TRIMBLE, M.D. Belf., late R.A.M.C.

C.B.E. (Civil)

EDWARD HOLBROOK DERRICK, M.D. Melb., F.R.A.C.P.
Deputy director, Institute of Medical Research, Queensland.

RONALD BRAMBLE GREEN, D.C.L. Durh., M.B. Lond., F.R.C.S.
Emeritus professor of anatomy and lately dean of medicine, King's College, University of Durham.

Major ALEXANDER CAMPBELL WHITE KNOX, O.B.E., M.C., M.B. Aberd.
Principal medical officer, St. John Ambulance Association; surgeon-in-chief, St. John Ambulance Brigade.

CHARLES HORNER GREER MACAFEE, M.B. Belf., F.R.C.S., F.R.C.S.I., F.R.C.O.G.
Professor of midwifery and gynæcology, Queen's University of Belfast.

JOSEPH ANTHONY MANCHÉ, M.D.
Vice-chancellor and rector magnificus, Royal University of Malta.

HARVIE KENNARD SNELL, M.D. Lond.
Director of medical services, Prison Commission.

CHARLES HERBERT STUART-HARRIS, M.D. Lond., F.R.C.P.
Professor of medicine, University of Sheffield.

TERENCE GEORGE WARD, M.B.E., M.R.C.S., F.D.S. R.C.S.
Dental surgeon, Queen Victoria Hospital, East Grinstead.

ARTHUR WARRINER WILLIAMS, M.D. Cantab., F.R.C.P.
Professor of medicine, Makerere College, Uganda.

ISABEL GRACE HOOD WILSON, M.D. Edin., F.R.C.P.
Principal medical officer, Ministry of Health; for services as medical senior commissioner, Board of Control.

O.B.E. (Military)

Surgeon Lieut.-Commander JOHN STUART PEPYS RAWLINS, M.B.E., B.M. Oxon., R.N.

Lieut.-Colonel GRAINGER WILSON REID, M.B. Edin., R.A.M.C.

O.B.E. (Civil)

WILLIAM FERGUSON ANDERSON, M.D. Glasg., F.R.F.P.S.
Regional consultant in diseases of old age and chronic sickness, Western Regional Hospital Board, Scotland.

ARTHUR GORDON WATERMAN BRANCH, M.D. Brist.
Senior medical officer (clinical), Plateau Hospital, Jos, Nigeria.

ERIC KENNEDY CRUICKSHANK, M.D. Aberd., F.R.C.P.
Professor of medicine, University College of the West Indies.

EDWARD MERRILLS DEARN, M.B. Sheff.
Commissioner, St. John Ambulance Brigade, East Riding of Yorkshire.

BRIAN OLIVER LYNDHURST DUKE, M.B. Cantab.
Senior medical research officer (grade II), West African Council for Medical Research.

RONALD GEORGE GIBSON, M.A. Cantab., M.R.C.S.
Member, Hampshire executive council local medical committee.

ERIC CHRISTIAN GILLES, DR.P.H. Johns Hopkins, D.SC. Maryland, L.R.C.P.E.
Formerly principal, Kano Medical School, Nigeria.

EDWIN CHARLES GIRLING, M.D. Edin.
Chairman, Holborn No. 1 National Service medical board.

RONALD BRODIE HEISCH, M.D. Cantab.
Senior specialist, medical department, and director of the insect-borne diseases division, Medical Research Laboratory, Nairobi, Kenya.

JOHN LEWIN, M.B. Lond., F.R.C.S., J.P.
Chairman, King's Lynn savings committee.

ALLAN STEWART MOODIE, M.B. Glasg.
Senior specialist (tuberculosis), Hong Kong.

BRYCE RAMSAY NISBET, M.D. Edin., F.R.C.P.E.
Medical officer of health, Kilmarnock.

DAVID EVAN PARRY-PRITCHARD, M.D. Lpool.
Country medical officer of health, Caernarvon.

UNA BEATRICE PORTER, M.B. Melb.
For social welfare services in Victoria, particularly under the auspices of the Young Women's Christian Association.

GEORGE FELIX RANDEGGER, M.B.E.
Medical director, Salvator Mundi Hospital, Rome.

KENNETH VANE ARNIM RODGERS, M.B.
For public services in the Bahamas.

JAMES ARNOLD WATERMAN, M.D. Glasg., F.R.C.O.G.
Formerly deputy director of medical services, Trinidad and Tobago.

KEITH DIGBY YOUNG, M.R.C.S.
Senior medical officer (clinical) in the former Somaliland Protectorate.

M.B.E. (Civil)

OSCAR ARNHEIM, M.D. Cologne
Medical officer, medical department, Swaziland.

EDGAR CECIL BANKS, L.M.S.S.A.
Lately deputy chairman, Preston No. 1 medical board, Ministry of Labour.

DAVID ERNEST TRUMPY, M.B. Melb.
Medical Superintendent, Ipswich Hospital, Queensland.

Surgeon Captain THOMAS TURNER, V.R.D., M.B. Lond., R.N.V.R. retd.
Chairman, Eastbourne Sea Cadets Corps unit.

Medical Education

TEACHING IN GENERAL PRACTICE

GERALD DELACEY
B.Sc. Wales, F.R.C.S.
GENERAL PRACTITIONER, BURGESS HILL, SUSSEX

As a rule, students in this country receive their medical training exclusively in hospitals, under the supervision of consultants who seldom have experience of general practice. Latterly however, the deans of several London medical schools have arranged for some of their students to work for a short time with a general practitioner, and for some years I have taken part in this training. It is, I believe, of increasing importance. Now that provincial towns have experienced consultants, and more patients can have skilled specialist treatment in hospitals near where they live, the amount and variety of clinical material at Metropolitan hospitals has become inadequate for the proper training of future general practitioners. Moreover, in general practice the student can often be shown on one day a number of patients illustrating a particular symptom or related condition, whereas in hospital he could not do this without attending several departments. In my practice there is of course the vast variety and amount of clinical material to be found in any large practice; but I have also a " pool " of patients with the following conditions, which are always available for demonstration:

Mongolism, microcephaly, hydrocephaly, and macrocephaly, congenital heart-disease; congenital dislocation of hip, Perthes' disease, and Pott's disease of spine; wasting of small muscles of hand, cervical rib, and peripheral nerve lesions; exophthalmic goitre, colloid goitre, myxœdema, and adenoma of thyroid; Parkinson's disease, paraplegias, hemiplegias, disseminated sclerosis, cerebral injuries, tertiary syphilis, congenital syphilis, and Huntington's chorea; familial acholuric jaundice; and of course a variety of herniæ, hydroceles, cysts of the epididymis, lipomata, sebaceous cysts, and so on.

The student must live in with the practitioner for at least a week. Apart from breakfast, he has all meals with the doctor's family, and accompanies the doctor in the surgery and on the rounds. The teacher should have a large practice including obstetrics, with adequate secretarial help; and in surgery hours at least two consulting-rooms should be available. The routine is as follows:

Work starts at 8.45 A.M. when the student examines the post, is instructed how to deal with the correspondence, and answers the telephone. He is trained to enter all messages at once in a book and to interpret messages (which are not always lucid). He attends the morning surgery, examines the patients, writes out the prescriptions which are dictated to him, and fills in various certificates, request for hospital appointments, and the like. He also helps to enter up notes in the record card.

At the end of surgery a certain amount of work must be done —e.g., writing of prescriptions, and arranging ambulances. After this the visiting list is drawn up and notes made, drawing attention to any special visits—e.g., Mrs. A. early, Mrs. Y. requires an injection of vitamin B_{12}—thus making sure that everything necessary is included in the doctor's bag.

Until lunchtime the student accompanies the practitioner on all his visits and notes how examinations are made in the home and explanations are given to patients and relatives. Almost without exception, patients are very pleased to be examined by their doctor and a student.

When morning visits are completed, a return visit is made to the surgery to note and attend to any further messages that have been taken during the morning.

In the afternoon the student spends at least an hour in the dispensing department of a busy chemist, where he is taught the basic principles of dispensing, and examines the various preparations of drugs in frequent use, such as digitalis, iron, and penicillin. Towards the end of the week he is allowed, under supervision, to make up certain prescriptions.

In the afternoons, too, he visits in turn the pathological, X-ray, physiotherapy, and obstetric departments of local hospitals so that he may know from personal experience the facilities available to doctors in general practice. Arrangements are made for him to meet the district nurses and health visitors so that he may know their views, ideas, and problems, and how they cooperate with the general practitioner.

In the evening the surgery is attended as in the morning, and any visits that have to be made after the surgery is finished. The student is expected to accompany the doctor on any night calls and on all emergency calls.

In the evening the student is encouraged to read about some of the conditions he has seen during the day and to read too the recent issues of the weekly medical journals.

These courses have been greatly appreciated by students, who say that in a week of my practice they have seen as much clinical material as they would in three months at their own teaching hospital. For me the students have been, without exception, a stimulus to my work and a source of enjoyable relaxation.

In England Now

A Running Commentary by Peripatetic Correspondents

I have erred, I have sinned, I cannot say you nay,
I have not seen a traveller since Empire Day,
Have earned the punishment and merited the pain—
No diaries this Christmas: I can not complain.
O Burroughs Wellcome, Glaxo, Sandoz, and Parke Davis,
My children cry without their little books—God save us,
I did not wish you harm—nor M & B, nor Nestlé.
Your New Year's fortune I can only wish depressedly.
An outcast doomed derided failure I should die
Had not one faithful soul retained eternally
(For no good reason) in his heart a warmer corner—
I thank you for your crimson book, O William Warner.

* * *

So term is ending at last, and the memories of its end should brace us for the holiday ordeal. But the nativity scenes yesterday were charming. All the actresses were 11 minus. The angels who worshipped the babe were white-robed and gilt haloed, their hair a spun glitter of brushed and shampooed gold, brown, and rich mouse. And, true to life, the prettier the angel, the more bent her halo. The madonna was exquisite black and ivory. Her classic features and blue and white wimple contrasting with Gabriel's gilt curls and chubby cheeks. She laboured prettily on her bale of straw, holding her head, for her slim 11-year-old body had no room for labour pains. The innkeeper's wife wrung her hands and blackbearded Joseph looked on—impassive. And then the babe was held and worshipped, as a new kitten or a tiny chick, by the breathless host of angels and brown-legged shepherds. And how did the serious seven-year-old in her school uniform get her tongue round the whole magnificat? And how did the choir manage to learn all those unfamiliar carols? But all those lovely angels—what a lot they have to live up to this Christmas. Better be a chorister—everybody knows what they are like off duty.

* * *

In an old Chinese torture, water drips slowly on to the victim's head, the relentless repetitive stimuli goading a frenzied nervous system to breaking-point. Such was the state in which I found a colleague on Christmas Day.

It all began on Nov. 5 when he rashly promised his four-year-old son a scooter for Christmas, provided his conduct in the interim was sufficiently exemplary to justify so lavish a gift. Thereafter, daily inquiries as to the advent of Christmas made increasing demands on my friend's self-control, culminating on Nov. 22 in a protracted, and at times falsetto, lecture to the effect that Christmas Day was synonymous with Dec. 25, which implied 33 days and 33 nights, 66 teeth-brushings, or the days needed to acquire 1*s.* 4½*d.* at the current rate of pocket money, and that further perseveration on the subject would invite stern counter-measures.

For the next thirteen days, this approach showed every sign of a well-earned success. Then, at the unfortunate time of 3.20 A.M., a small voice was heard to say: "Daddy, is it Christmas yet?" The resulting upheaval, awakening neighbours in four directions and causing many raised eyebrows on the train and curious glances in the launderette later that morning, can only be described as appropriate to minimising further miscalculations by a child reputed to be able to count to 100.

An uneasy peace reigned until Dec. 12, when, choosing the top of a crowded bus where chastisement could confidently be expected to arouse public hostility, the child observed half rhetorically "Christmas is a long way off, isn't it?" which, under the circumstances evoked nothing more than a monosyllabic assent and a somewhat excessive display of teeth. Fresh violence did not break out until the morning of Dec. 18 when, for an unaccountable reason, the wretched juvenile suddenly leapt out of bed and ran excitedly round the house yelling "Yippee, it's Christmas!". This provoked a course of action at once salutary and inhibitory to all further interest in the festive season.

As the appointed day approached, this conditioned apathy gave rise to concern and, inevitably, a remorseful parent sought to make amends by getting the finest scooter to be had. This was produced in all its glory on Christmas Day. The only comment its recipient made was: "I don't think I want a scooter any more, Daddy. Can I have a tricycle for next Christmas?"

* * *

In the cold and wet weather now with us, it is pleasant to recall the few hot days of last summer. It was on such a day that I was called to do an emergency cæsarean section at our local maternity unit. On these occasions I have to change in the admission bathroom, which has a separate lavatory off it, which can only be reached through the bathroom.

I duly changed, carried out the cæsarean, and, as it had been extremely hot in the theatre, returned to the bathroom intent on having a cold bath. I turned on the cold tap, undressed completely, opened the lavatory door and stepped inside to spend a penny; to my horror, and to hers too, I was standing naked before a pregnant woman sitting on the lavatory seat.

I jumped back into the bathroom, shut the door, and shouted "Are you all right?" A small voice answered rather tremulously "Yes." As I jumped into the bath I shouted, "I will be out of here in two minutes." A minute later I was out of the bath and as I reached for my towel, a shrill voice broke through from the lavatory, "Oh! My baby's come". Simultaneously she rang the emergency bell in the lavatory; seconds later two panting midwives burst through the door, rushed into the para-4, and assisted with delivery of no. 5 from the lavatory pan. Only later did they notice, with faint surprise, the nude male figure clasping a towel round his midriff and shaking with uncontrollable laughter.

Apparently a little known treatment of uterine inertia is for the medical attendant to undress?

* * *

Seeing patients daily in a polyglot outpatient clinic, one becomes acutely aware of the cross-currents of national sentiment. It is an experience to which every diplomat should be exposed, early in his career, so as to desensitise him a little. For the psychiatrically conscious doctor, too, it is a revelation to see how constant are the basic human quandaries and how independent they can be of language or of cultural background. This is not to deny that certain countries may favour some of the classical situations above others—it is merely that they seem to crop up everywhere, in every tongue. The odd thing is that the detection of an emotional problem seems not harder but easier when doctor and patient have their only common ground in a language unfamiliar to one of them. In these circumstances the keystones of the patient's personality stand out more obviously, it seems, than when the architecture is obscured by all the curlicues and adornments of neurotic deceit which sprout when both are of the same mother-tongue. It is almost as though the patient is unconsciously trying to make the message clearer, from some dim atrophic instinct of fair play.

In our cosmopolitan atmosphere, every patient is a plot for a novel—alas, usually one which has been written before. Reading this literature every day one is a little in danger of reaching the point where the most deeply observed and sensitive novels ever published only wake in one the thought that the hero (or the author) could do with a few pills—dexamphetamine with amylobarbitone for Oblomov, chlorpromazine for Kafka's heroes, phenobarb for Prince Myshkin. Lolita, in different case, perhaps suggests occupational therapy, and, for that gamekeeper, speech therapy might be appropriate. The list is endless, but luckily there are always the sore throats and diarrhœas to bring one back to earth.

* * *

THOUGHT FOR THE NEW YEAR

In this age of goonery,
Take-over tycoonery,
Racial riots,
Reducing diets,
Factors rhesus,
Credit squeezes,
Ambridge Archers,
Aldermaston marchers,
Rocket ranges
And winds of changes,
Thank God for divers
Tranquillisers.

Letters to the Editor

WHAT IS EARLY MITRAL STENOSIS?

SIR,—The letter from Dr. Cotes and his colleagues (Dec. 17) suggesting a controlled trial of medical versus surgical treatment in early mitral stenosis raises the fundamental question—what is early mitral stenosis? Is it to be defined anatomically, hæmodynamically, on the basis of clinical examination, or on the basis of symptoms? The Cardiff workers appear to use symptoms as the criterion, defining early mitral stenosis as established stenosis with "*few* symptoms other than *moderate* breathlessness on exertion". I would criticise such a definition on the ground that mitral stenosis may reach an advanced and potentially fatal degree with *no* symptoms other than *slight* breathlessness on exertion.

Three weeks ago, I saw a woman aged 31, thirty weeks advanced in her second pregnancy, who had had no trouble during her first pregnancy four years previously, and no abnormal dyspnœa until a few weeks before I saw her when she started coughing blood. She had the signs of established severe mitral stenosis with sinus rhythm, and I referred her to Mr. Peter Brunnen for mitral valvotomy. At operation the mitral orifice was extremely small, measuring only 7·5 mm. in diameter. Was this early mitral stenosis?

Five years ago, I saw a woman aged 24, who had been referred to hospital by her doctor for consideration of mitral valvotomy. She had the signs of established mitral stenosis with sinus rhythm but virtually no symptoms. Operation was not recommended, on the ground that her symptoms were too slight. She was seen again as an outpatient five months later when she was twelve weeks pregnant. At this time she was doing all her own housework and only admitted to slight incapacity. Five weeks later she was readmitted in acute and fatal pulmonary œdema. At necropsy her mitral orifice measured 10 mm. in diameter. As there was no naked-eye evidence of recent inflammation of the valve, it is reasonable to assume that the mitral stenosis was of substantially the same severity when the patient was seen five weeks previously. Clearly this was not early mitral stenosis.

There seems to me to be irrefutable evidence that mitral stenosis sometimes reaches an advanced and potentially lethal degree without giving rise to more than slight dyspnœa on exertion. I believe, therefore, that if there is clinical evidence of severe mitral stenosis, valvotomy should be urged even if symptoms are minimal. This applies with special force to women of childbearing age who are in sinus rhythm.

Aberdeen. D. S. SHORT.

ATHEROSCLEROSIS AND CORONARY (ISCHÆMIC) HEART-DISEASE

SIR,—Dr. Prior [1] draws the conclusion from publications of this unit [2 3] that ischæmic heart-disease in the young has a different pathology from ischæmic heart-disease in the old. Actually, no such analysis of the material available to us has yet been made. Routine tabulations do not support Dr. Acheson's interesting suggestion [4] that acute coronary thrombosis is the important factor during early middle age but coronary atheroma in older persons:

Deaths from Ischæmic Heart-Disease, National Necropsy Survey, Great Britain, 1954–56, Males

Coronary arteries	*45–59 years*	*60–70 years*
Much coronary atheroma (no.)	475	591
Recent coronary thrombosis present	*49%*	*46%*
Moderate or little coronary atheroma (no.)	53	53
Recent coronary thrombosis present	*51%*	*49%*

1. Prior, A. P. *Lancet*, 1960, ii, 817.
2. Morris, J. N. *ibid.* 1951, i, 1, 69.
3. Morris, J. N., Crawford, M. D. *Brit. med. J.* 1958, ii, 1485.
4. Acheson, R. M. *Lancet*, 1960, ii, 706.

Throughout 45–70 there is a small minority, perhaps 10% of deaths ascribed to ischæmic heart-disease, in which there is not much (i.e., widespread, confluent) coronary atheroma; the fraction may be 20% in deaths from a first infarction (no ischæmic myocardial fibrosis being present). But a preliminary scrutiny has disclosed only one very small group that fits Dr. Acheson's hypothesis, sedentary and light workers aged 45–49 dying in a first infarction and with a recent coronary thrombosis. Among 11 such cases, only 4 or 5 showed much coronary atheroma and in none was calcification reported. The hint is interesting in light of previous observations.[5 6] Be that as it may, there is no indication in the above figures of any gross difference in the ischæmic heart-disease of young and old.

It is important that the main issue should not be obscured. This is the suggestion repeatedly emerging from epidemiological studies that coronary thrombosis, and coronary occlusion in general, is not just a simple or direct function of coronary atheroma. Coronary occlusion arises on a basis of coronary atheroma; but these seem to represent two distinct "diseases" of the coronary arteries—one with plaques in the walls and the other occluding the lumen—which are related but not the same. Mural atheroma is of course a patchy and disseminated; lumen occlusion a localised, focal condition. Moreover, it is common at postmortem for gross mural disease to be seen without occlusion, whereas occasionally cases arise like the 11 just described with complete occlusion and minor mural involvement. Experimentally, it has proved far more difficult to produce occlusive coronary thrombosis than fatty lesions of the coronary intima.[7–11]

The epidemiological evidence from this unit on the distinction between disease of the wall and disease of the lumen may be summarised as follows. Where findings are clearer in early than later middle age they are given for 45–59 years. Macroscopic evidence alone is reported.

(1) In the necropsy material of the London Hospital,[2] now studied in more detail, coronary-mural atheroma was an almost invariable finding before the first world war, many men showing widespread disease. But frank thrombosis of the coronary arteries, and severe coronary stenosis, apparently were uncommon. The suggestion from these records of the *recent history* of coronary disease is that during the past half-century the prevalence in the population of coronary occlusion (and ischæmic heart-disease) has increased, but not the prevalence of coronary atheroma:

Coronary-artery Disease, 1908–56, Males, aged 45–59

Coronary arteries	*Deaths from injuries, infections, cancer, &c.*		*Deaths from hypertension, cerebrovascular disease, &c.*	
	1908–13 (530 cases)	*1954–56 (1394 cases)*	*1908–13 (87 cases)*	*1954–56 (292 cases)*
	%	%	%	%
Coronary atheroma: Moderate	53	34	36	32
Much			40	30
Calcification	19	10	26	22
Coronary stenosis	4·2	13	10	28
occlusion	0·8	2·1	1·1	5·5
Ischæmic myocardial fibrosis present	1·3	4·4	3·4	17

1908–13, London Hospital; 1954–56, National Necropsy Survey.

Average annual no. of deaths from ischæmic heart-disease with recent coronary thrombosis, males, 45–59, London Hospital, 1908–13 = 1·2 and 1954–58 = 4·2.

(2) Coronary-lumen occlusion arises on the basis of coronary-mural atheroma, and an increase of atheroma is usually accompanied by an increase of occlusive disease. This is seen, for example, as age advances and in hypertension which is associated characteristically with gross increase of mural

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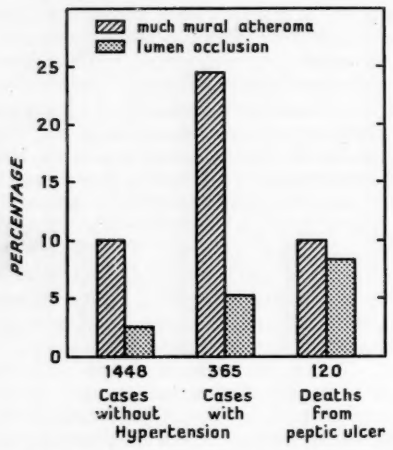
6. Morris, J. N. *Arch. intern. Med.* 1959, **104**, 77, 903.
7. Crawford, T., Levene, C. I. *J. Path. Bact.* 1953, **66**, 19.
8. Florey, H. *Brit. med. J.* 1960, ii, 1329.
9. Harrison, C. V. Recent Advances in Pathology. London, 1960.
10. Thomas, W. A., Hartroft, W. S. *Circulation*, 1959, **19**, 65.
11. Gresham, G. A., Howard, A. N. *Lancet*, 1960, ii, 527.



Coronary atheroma and coronary occlusion, National Necropsy Survey, deaths from causes other than ischæmic heart-disease, males, aged 45–59.

atheroma.[9] Analysis of the condition of the coronary arteries in various *diseases*, however, reveals another instance of dissociation of lumenal from mural pathology. In deaths from peptic ulcer, gastric and duodenal, there was a greater prevalence of coronary occlusion but no increase in the prevalence of mural disease ($P < 0.002$) (see figure).

There is a tantalising hint of something of the same kind in the London Hospital records before the first world war. Among 24 male deaths from diabetes the amount of mural atheroma at 45–59 years and at 60–70 was about the same as in the deaths from hypertension and cerebrovascular disease. However, Turnbull noted 3 times as much coronary stenosis, coronary occlusion, and ischæmic myocardial fibrosis among the diabetics. Diabetes was also important in at least two of the small number of deaths from ischæmic heart-disease. (It is worth speculating about high-fat diets—e.g., Allen and Sippy.[10])

(3) There does not appear to be any particular relationship in this country between coronary atheroma, *occupation*, and *exercise*, but a trend has been found in coronary occlusion. Sedentary and light workers show proportionately more recent fatal thrombosis than active, and active more than heavy workers; it is similar with complete or near-complete closure of coronary arteries in other deaths [3] ($P < 0.002$):

Coronary-artery Disease and Occupation, National Necropsy Survey, Deaths from Causes other than Ischæmic Heart-disease, Males, aged 45–70

Coronary arteries	*Occupation*		
	Light (1392 cases)	*Active (1377 cases)*	*Heavy (836 cases)*
	%	%	%
Much mural atheroma	21	17	18
Calcification present	23	20	21
Lumen occlusion	5·9	4	3·1

(4) Setting up a " model ", from the necropsy data available to us of the contemporary *distribution in the population* as a whole of coronary atheroma and coronary occlusion (it is necessary to include a proportion with ischæmic heart-disease as well as the categories of the second table above) there seems again to be a difference, particularly in early middle age. Thus the great majority of men show mural disease at necropsy, mostly a little or moderate amount; but only a minority of men seem to have naked-eye narrowing of a main coronary artery, and in most of these it is severe.

In the above statement " atheroma " has been equated with " mural disease "; for simplicity, these terms are preferred to " atherosclerosis ". Complete or near-complete closure of a main artery and recent frank thrombosis are regarded as " coronary occlusion ". There is no difficulty in reconciling these observations with Duguid's school,[13 14] a crucial proposition of which is that important coronary obstruction is usually due to thrombosis and organised thrombus whatever the nature of mural plaques. In this connection it is worth remembering that in most deaths from ischæmic heart-disease there is gross coronary stenosis—the result very likely of previous thrombosis—in one or more main arteries.[15] It may thus be misleading to lay too much stress in the pathology on the presence of *recent* thrombosis.

To sum up, coronary occlusion arises on the basis of coronary atheroma, and with more atheroma there tends to be more occlusion. But over and above that, other " causes " are importantly involved in producing occlusion, causes unrelated to the atheroma. Coronary atheroma is only one element in coronary occlusion: it is necessary but not sufficient. If this is true in whole or part there are theoretical and practical consequences. For example, it may be postulated that the " modern epidemic " is of coronary thrombosis and not of coronary atheroma; and this offers more than one route to prevention—by correcting recent faults in the way of life that have produced an increase of the former, or longer established habits involved in the persistence of the latter.

We are greatly obliged for much help given us over the years.

Medical Research Council,
Social Medicine Research Unit,
London Hospital, E.1.

J. N. MORRIS
M. D. CRAWFORD.

12. Briggs, R. D., Rubenberg, M. L., O'Neal, R. M., Thomas, W. A., Hartroft, W. S. *Circulation*, 1960, **21**, 538.
13. Duguid, J. B. *Lancet*, 1954, i, 891.
14. Duguid, J. B., Robertson, W. B. *ibid.* 1955, i, 525.
15. Crawford, T. Pathogenesis and Treatment of Occlusive Arterial Disease: Proceedings of Conference, Royal College of Physicians, 1959; p. 143. London, 1960.
16. Hadgraft, J. W. *Pharm. J.* 1960, **184**, 277.
17. Sherlock, S. *Practitioner*, 1960, **185**, 492.

ORAL POTASSIUM SALTS

SIR,—We were interested to read in your annotation of Dec. 17 on diuretics that an effervescent tablet was recommended as a convenient and palatable form of administering potassium salts. These tablets contain potassium bicarbonate, potassium acid tartrate, and anhydrous citric acid as described by Hadgraft,[16] and they have been recommended by Professor Sherlock.[17] We have been given a supply of these tablets by Mr. Hadgraft, and we entirely agree that they are the most pleasant way of administering potassium salts yet devised. Pharmacy departments in most hospitals, however, have not got facilities for preparing the tablets, and we have not yet been able to persuade any manufacturing pharmaceutical firm to make them for us.

The administration of potassium is widespread to prevent hypokalæmia in patients receiving the benzothiadiazine group of drugs, and it is important that they should be effective. It is often given as enteric-coated tablets of potassium chloride, occasionally when simple tab. pot. chlor. has been prescribed. Furthermore, in some of the compound tablets of the benzothiadiazine group with potassium chloride, the salt is in an enteric-coated inner kernel, from which it may not be absorbed.

We have demonstrated a complete failure of absorption of potassium in a patient with hypokalæmia and in a healthy adult, both of whom were given enteric-coated potassium chloride. We returned some of these tablets to the well-known firm who made them, and we received the reply that they fulfilled the official tests laid down by the *British Pharmacopœia*, as though this excused the fact that they were not absorbed in vivo.

We should like to draw the attention of all doctors to the possibility that enteric-coated tablets may be ineffective, and we hope that the *British Pharmacopœia* will investigate their standards and lay down new ones that will ensure that all such preparations will be effective in vivo. Finally,

we should be very pleased to hear from any pharmaceutical firm who would be interested in manufacturing Hadgraft's tablets, for we feel that they are a real advance towards the palatable administration of potassium salts, and we think there would be a wide demand for them following the lead of your annotation.

Lewisham Hospital, London, S.E.13. J. S. PIRNIE
J. S. STAFFURTH.

THE GENERAL PRACTITIONER AND THE HOSPITAL

SIR,—Several correspondents have recently drawn attention to the increasing exclusion of general practitioners from hospital, and have indicated that in some areas simple X-ray and pathological facilities are not available to them. As Professor Rodgers has inferred,[1] this can lead to lowering of standards of general practice.

Many colleagues with hospital experience and perhaps a diploma in one of the specialties, and with a genuine interest in good general practice, are deterred from entering practice by the prospect of losing hospital contact. Indeed, for this reason many potentially excellent general practitioners are leaving Britain to work abroad.

It has been suggested that the £1 million "reserved money" could be used to imburse clinical assistant posts, particularly at peripheral hospitals where there is often a shortage of junior staff. Here the suitably experienced general practitioner could play a useful part in the specialist team. If the suggestion was adopted, I feel it would not only maintain a high standard of general practice but also quell the insidious exodus of young doctors abroad.

Bournemouth. DENIS R. COUCHMAN.

EXTERNAL CARDIAC MASSAGE

SIR,—This is to report the successful use of external cardiac massage, believed to be the first case reported in this country. Interest in this procedure was stimulated by recent editorial comment [2 3] and by Ross [4] who had recently discussed the technique with the innovators at the Johns Hopkins Hospital in Baltimore. The method depends on the integrity of the heart as a unidirectional pump, pressure on the sternum, depressing it 5–7 cm., compressing the heart and emptying it while relaxation with consequent negative intrapleural pressure allows the heart to fill. The method has the further advantage of artificially ventilating the patient's lungs. Some scepticism had been felt about external cardiac massage as it was believed time would be lost before instituting adequate circulation. There are many circumstances, however, where thoracotomy is not practicable, as in single-handed surgery where this form of massage may well restart the heart or at least maintain a circulation until expert aid can be summoned.

A man of 44 had a mitral valvotomy on Dec. 19, 1960 (Mr. R. H. F. Brain), for mitral re-stenosis complicated by atrial fibrillation and recurrent emboli, one of which had induced a hemiplegia. On Dec. 20, after an uneventful night, he vomited and inhaled vomitus. His condition deteriorated rapidly and an emergency tracheostomy was performed. As respiratory exchange was inadequate, he was ventilated on a Barnet respirator. On Dec. 21, during the afternoon, cardiac arrest occurred when the respirator was removed for tracheal toilet. Reopening of the chest was thought inadvisable in this case because of multiple emboli, hemiplegia, and aspiration pneumonia. External cardiac massage was commenced at 60 impacts to the minute while ventilation was performed manually with a Boyle's anæsthetic apparatus. A carotid pulse was felt immediately and after ten minutes massage the patient started involuntary gasping movements. After twenty minutes a palpable apex-beat was present, as were femoral pulses. Blood-pressure at this stage was 90/50 mm. Hg with a regular pulse-rate of 80. The pupils, which had dilated, returned to normal size. The patient's tracheostomy tube was reconnected to the respirator, with a tidal volume of 500 ml. Three hours later he was maintaining his blood-pressure and pulse but appeared to have suffered cerebral damage.

Unfortunately the patient died after twenty-four hours, without rousing. An arrest during this time was restarted by the same technique. It was impressive that an adequate circulation could be maintained and normal heart action restored. Adequate ventilation is most important.

I wish to thank Mr. R. H. F. Brain for permission to publish details of this case.

Guy's Hospital, London, S.E.1. P. J. MOLLOY.

1. Rodgers, H. W. Address at Institute of Clinical Science, Queen's University, Belfast, Nov. 1, 1960.
2. *Brit. med. J.* 1960, ii, 1582.
3. *Lancet*, 1960, ii, 1333.
4. Ross, D. N. Personal communication, 1960.

THE OXFORD CLINICAL SCHOOL

SIR,—The Nuffield professors complain that there are not enough students and that their calibre is not high enough. They may be interested to know the reasons why they lost one promising student.

A young relative of mine is according to her headmistress well above average, and she has in fact since been accepted for training in medicine at Cambridge. She would have applied to Oxford but for two things. First, the university will not give exemption from its preliminary examination in natural science (which corresponds to the 1st M.B. examination of some other universities) on the advanced-level General Certificate or any other examination. This implies the strain of sitting another examination, more fees, and more time. Secondly, the clinical course is prolonged by six months spent in the study of pharmacology, pathology, and bacteriology. This also implies the expenditure of more time and money. It means that all students take an honours degree, and there might be some excuse for this if there were any evidence that it produced better doctors. I have seen no such evidence, and your annotation of Dec. 17 shows that even the authorities at Oxford can find none. Moreover, other universities seem able to arrange for students to take an honours degree, as well as to study these subjects, during a normal three years' course.

AN ANONYMOUS CANTAB.

ORAL TREATMENT OF PERNICIOUS ANÆMIA WITH LOW DOSES OF H.P.P./1

SIR,—Dr. Mooney and Dr. Heathcote (Dec. 17) have missed the main point of my letter of Nov. 19. Clinically, B_{12} deficiency presents a broad spectrum which may extend from mental illness on the one hand to tobacco amblyopia on the other. Included in this spectrum are pernicious anæmia and subacute combined degeneration of the cord, but they represent only two facets of the problem and may not be present when the others are.

They refer to H.P.P./1 therapy as "a highly acceptable hæmopoietic agent" but this in no way means that they are correcting deficiency of vitamin B_{12}. If they think they are I would welcome their explanation about cases of subacute combined degeneration of the cord which occur in the absence of anæmia. Furthermore, would they be prepared to treat such cases with oral B_{12} peptide? And if they are not prepared to treat such cases with oral B_{12}, why not?

Finally, in this instance I am not concerned about the patient's enthusiasm for different modes of treatment. Until it has been shown that oral B_{12} peptide alleviates all forms of vitamin-B_{12} deficiency, and also that all such

patients will cooperate 100% by taking such treatment regularly for the rest of their lives, I shall continue to give it in big doses intramuscularly as a sop to my own enthusiasm. I agree that it is difficult to draw conclusions from serum-B_{12} levels alone but humbly suggest that it is safest to err on the side of caution. When penicillin was in short supply it was found that 20,000 units 8-hourly would heal the primary chancre of syphilis very rapidly and effectively mask the development of the secondary stage. The appearance of many cases of neurosyphilis following this line of therapy, however, soon produced a radical change in dosage. As far as I am aware there is no shortage of vitamin B_{12}, and I quite fail to see the advantage of giving minute doses of an oral preparation which remains unproven in its long-term effects and which may produce irreversible damage in the central nervous system long before this becomes clinically apparent.

Institute of Clinical Research,
Middlesex Hospital Medical School,
London, W.1. A. D. M. SMITH.

ADMINISTRATION IN MENTAL HOSPITALS

SIR,—To be placed in a position of authority is a stern test of capacity and character. If I read Dr. Bardon's letter of Dec. 17 correctly, it would appear that many consultants in psychiatric hospitals are anxious to remove this position of authority from medical superintendents and to partake of it entirely by vote of their medical staff committees or partially as independent chiefs of service superintending their own particular units and answerable to no-one, not even their own juniors.

It is to be hoped that if they are successful in their anarchic ambitions, if they be such, they will eventually be able to bear the full glare of public scrutiny of their work and devotion to duty which is now so assiduously being turned on us rather weary, long-suffering medical superintendents.

Harpenden,
Herts. HAROLD PALMER.

SIR,—Whilst, as Dr. Bardon implies, the style of motivation does not necessarily establish the desirability or practicability of a new system of administration, I do not believe it can be maintained that an analysis is of no value.

It is true that human beings driven by worthy motives have sometimes effected indifferent or even disastrous situations, and, on the other hand, persons with unworthy motives have, on occasion, produced (to their own amazement or chagrin) excellent end-products. Nevertheless, the fact that the vast majority of us admire and respect the former rather than the latter type of personality must surely have an important significance.

Leaving aside a minority who suffer from some peculiar chip on the shoulder, the motivations in this squabble are not so deeply unconscious—they are the common-or-garden lusts for money and power. Medical superintendents have been awarded an extra £250 per annum. They do not wish to lose this, and other consultants suffer from feelings of envy. By dividing a mental hospital into two to six separate divisions (depending on the number of established consultants), every consultant hopes to be able to claim some or all of an extra "responsibility grant"; and each consultant will also satisfy his lust for power by becoming a superintendent, even if of a lesser domain.

Human motives are generally mixed, altruistic fusing with selfish; but the peculiar fact is that in the many published letters nobody has tried to prove that patients would become more comfortable or happy under any of the new systems suggested. It certainly cannot be denied that patients in the hospitals mentioned by Dr. Russell Barton (Dec. 17)—and in many others—have had their lot considerably improved through the energetic leadership of dedicated medical superintendents.

It is high time someone in authority explained that the essential function of mental hospitals is to serve the interests of patients, and not merely to please the whims of consultants or medical superintendents.

ANALYST.

PNEUMOCONIOSIS

SIR,—Dr. Oakley (Dec. 24) makes some interesting observations on uncertifiable pneumoconiosis. His conclusions, however, are dependent upon the proposition that there is such a condition.

Certifiable pneumoconiosis is defined in the Industrial Injuries Act. "Pneumoconiosis means fibrosis of the lungs due to silica dust, asbestos dust or other dust and includes dust reticulation." There are many medical arguments intended to show that this is not a good definition; nevertheless certifiability would seem to be a matter of law, and this is the only legal definition. If this is not so, can Dr. Oakley or anyone else give a *legal* definition of category 1 or less (uncertifiable) pneumoconiosis?

If, as some people think, Parliament intended and the Act provides that pneumoconiosis is certifiable as soon as it is diagnosable then Dr. Oakley's reproof is surely misdirected.

I am well aware that a man with category-1 pneumoconiosis whose disability does not exceed a purely nominal 1%, who is 64, and who has worked in a dusty trade for 50 years is likely to die of some other condition before he comes to serious harm from his pneumoconiosis, but what of the man of 25 who has worked in dust for only 5 years? Can we be so sure about him? Parliament intended that he should be protected—can we be sure that he is?

Halstead,
Essex. R. E. W. FISHER.

NO CHAIR OF PSYCHIATRY

SIR,—May I refer to a matter which causes considerable concern to psychiatrists in the Midlands—namely, the continuing failure of the University of Birmingham to appoint a professor of psychiatry.

Until a couple of years ago, Birmingham had, oddly enough, a professor of experimental psychiatry, but since Professor Elkes vacated this post a successor has not been appointed. Just why Birmingham has not followed most other universities in appointing a professor of psychiatry has never as far as I know been publicly disclosed, and your journal would seem to be the appropriate place for a statement from the university on this important matter.

There can be little doubt that the absence of a chair in psychiatry and the consequent absence of postgraduate instruction in the specialty prevents promising candidates from seeking posts in the hospitals of the Birmingham region and partly accounts for the poor psychiatric standing of the region in relation to other more progressive regions.

Powick Hospital,
near Worcester. A. M. SPENCER.

CRYPTOGENIC LIVER ABSCESS

SIR,—Colonel Said Ahmad, of Karachi, stated [1] that "the amœbic and non-amœbic varieties of abscess are distinguished by the naked-eye characteristics of the pus, since amœbæ are usually not recovered even from known amœbic abscesses".

Both of these statements call for comment, in that a

1. *Lancet* 1960, i .1195.

small undisturbed amœbic liver necrosis yields, not infrequently, only white or yellow pus, and it is only when the trabeculæ and walls of the necrotic area have been disturbed that characteristic "anchovy" pus appears. Further, by the use of an appropriate technique, such as digestion of the pus 'Varidase', the proportion of amœbic "abscesses" which yield amœbæ is of the order of 90–100%.

It will be noted that the word abscess has, to a certain extent, been avoided, in that the lesion in the liver due to invasion by the amœbæ is not a true abscess, and should preferably be known as amœbic liver necrosis.

Amœbiasis Research Unit,
Institute for Parasitology,
Durban.

R. ELSDON-DEW.

COLD INJURY AMONG CHILDREN SEVERELY ILL IN THE TROPICS

SIR,—Dr. Morley's article (Nov. 26) will, I hope, be widely read. Coldness of the extremities is so easy to appreciate in the tropics, and is still so rarely observed. Many sick children develop subnormal temperatures, but this is most typically true of kwashiorkor. "In the Gold Coast patients, coldness of the extremities was very important. Even in an equatorial climate this sign was conspicuous. Keeping the child warm was found to be one of the most important points in treatment of all the advanced cases. A radiant heat cradle would facilitate treatment in no uncertain degree." [1]

Close contact with the mother, as Dr. Morley says, may be essential. But, failing this, a radiant-heat cradle is easy to construct wherever electricity is available, and hot-water bottles can be used where it is not. I found that with 2 or 3 of these cradles in the wards in Kumasi the results of treatment were greatly improved. I have often tried to persuade other doctors to use radiant heat for these cases, but it seems difficult to convince them that with an atmospheric temperature of 95°F or more, a sick child may be suffering from cold injury.

American University
of Beirut,
Lebanon.

CICELY D. WILLIAMS.

NEW IDEAS ON EPIDEMIC VIRUS INFECTIONS

SIR,—In the matter of Dr. Garvie's letter of Dec. 31 advocating fresh air in the treatment of influenza, may I recount another incident from the 1918 epidemic?

I was ship's surgeon on s.s. *Remuera* and we had on board a battalion of New Zealand troops bound for England. After several days in Halifax where the troops went ashore and where "Spanish influenza" was present, we sailed in convoy with twenty other ships on July 20, 1918. Our epidemic started on July 23 and in the next few days we had hundreds of cases. The medical officer to the troops, a courageous young man, one Lieutenant Wishart, and I decided to bed and treat them on deck and we got the mate to screen off the starboard promenade deck. It was rather cold, there were icebergs about, and we were not popular, but, having been a patient at Frimley Sanatorium some years before where, in the spartan regime existing then, snow on the bed was a laughable triviality, I had no fears of fresh air. Whereas other ships in the convoy kept dropping out to sink their dead (whether for religious or nautical reasons I never understood), one ship losing about 30, we did not lose a man and sent only 1 to hospital when we got to Liverpool—an officer, who had been treated in his cabin—with what I now recognise to have been a mild encephalitis.

Since then I have repeatedly found that when one can treat early influenza in bed in open-air conditions it is a minor malady without complications and little hangover. How the respiratory mucous membrane uses its birthright of fresh air to repel viral invaders is beyond me, but it does.

Beckley,
Rye, Sussex.

C. G. LEAROYD.

1. Williams, C. D. *J. Amer. med. Ass.* 1953, **153**, 1280.

HARTNUP DISEASE AND CYSTINURIA

SIR,—We are grateful for the favourable comments on our paper on Hartnup disease in your editorial of Dec. 24. In this article we suggested that the signs and symptoms of the condition were due to impaired transport of many monoamino-monocarboxylic aminoacids by the cells of the proximal renal tubules and by the jejunal cells. The results proved that tryptophan was poorly absorbed in the small intestine, and in addition gave suggestive but not conclusive evidence for impaired absorption of tyrosine. Transport of other aminoacids was not investigated because of the difficulties in the performance of large numbers of metabolic tests in a limited number of patients.

We were originally unwilling to reject the possibility previously suggested by Nemeth and Nachmias [1] of reduced action of the enzyme tryptophan pyrrolase because the patients excreted abnormally low amounts of kynurenine after oral tryptophan. This result has since been supported by Hersov and Rodnight,[2] who found a reduced output of kynurenic and xanthurenic acids. A dosage of tryptophan (70 mg. per kg. body-weight) was fortuitously chosen for our tests, but unfortunately at this dosage there is great variation in kynurenine excretion as related to the rate of tryptophan absorption. Since patients with Hartnup disease absorb tryptophan abnormally slowly, the experimental results are fully explained by the intestinal defect in the disease. There is thus no need to invoke deficiency of tryptophan pyrrolase. We agree that use of injected tryptophan would solve the somewhat equivocal results from administration of tryptophan by mouth.

As you state, tryptamine is more likely to cause the neurological symptoms of the disease than are absorbed indolic acids. Indole is another toxic substance formed in excess in Hartnup disease, and is equally likely to cause the cerebellar ataxia present in exacerbations of the condition. Both indole and tryptamine are rapidly converted to less toxic substances by enzymes within liver cells. Tryptamine is oxidised to indolylacetic acid by monoamine oxidase, and indole to indoxyl by the non-specific enzymes of the microsomal fraction. Monamine-oxidase inhibitors are therefore contraindicated in Hartnup disease, and iproniazid would be especially dangerous since it inhibits the microsomal enzyme systems in addition.[3] These drugs might easily be prescribed to combat the psychological depression which has been a prominent feature of exacerbations of the disease. The most comprehensive modern review of Hartnup disease has now been published by Jepson and Spiro,[4] the former being one of the team who originally described the condition.

In the last sentence of your editorial you predict that analogous clinical conditions to Hartnup disease will be described in the future. We, however, think they have already been described. Experiments in dogs [5 6] suggest that aminoacids are transported by the proximal tubular cells of the kidney from the tubular lumen to the renal capillary blood in three distinct groups. These groups are: group 1, the dibasic-monocarboxylic aminoacids, lysine, ornithine, and arginine; group 2, the monoamino-monocarboxylic acids with the important exception of glycine; group 3, glycine alone. Hartnup disease is probably a

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2. Hersov, L. A., Rodnight, R. *J. Neurol. Psychiat.* 1960, **23**, 40.
3. Brodie, B. B., Gillette, J. R., LaDu, B. N. *Ann. Rev. Biochem.* 1958, **27**, 427.
4. Jepson, J. B., Spiro, M. J. The Metabolic Basis of Inherited Disease (edited by J. B. Stanbury, J. B. Wyngaarden, and D. S. Fredrickson). New York, 1960.
5. Beyer, K. H., Wright, L. D., Skeggs, H. R., Russo, H. F., Shaner, G. A. *Amer. J. Physiol.* 1947, **151**, 202.
6. Kamin, H., Handler, P. *ibid.* 1951, **164**, 654.

specific disorder of transport of group-2 aminoacids. Transport of the group-1 aminoacids plus cystine (a diamino-dicarboxylic aminoacid) by the renal tubular cells has been shown to be defective in the more common disease, cystinuria.[7] If cystinuria is to be regarded as analogous to Hartnup disease it must be proved that transport of the involved aminoacids is defective in the small intestine as well as in the kidney.

We have recently shown [8] that transport of lysine and of ornithine by the jejunal cells in homozygous cases of cystinuria is grossly impaired. After a large oral dose of these aminoacids, a considerable fraction escapes absorption and appears unchanged in the fæces. By contrast, normal subjects absorb the aminoacids completely except for a few individuals in whom the substances produce intestinal hurry with watery diarrhœa. In the cystinuric patients, some of the unabsorbed lysine or ornithine is broken down by colonic bacteria to the diamines, cadaverine or putrescine. Urinary excretion of the diamines in cases of cystinuria was first described by von Udransky and Baumann [9] in 1889, and was reviewed in detail by Sir Archibald Garrod [10] in his famous Croonian lectures. Garrod obviously thought that diaminuria in cases of cystinuria was of major importance, as one of the chapters in his classical monograph *Inborn Errors of Metabolism* [11] was entitled Cystinuria and Diaminuria.

The true significance of diaminuria in cystinuria has, however, remained unexplained until the investigations of Hartnup disease gave the essential clue that jejunal transport of aminoacids could be defective. Garrod was always puzzled by the great variability of diamine excretion by cystinuric patients.[12] Modern knowledge of the metabolism of cadaverine and putrescine gives the explanation. These diamines are rapidly oxidised in the body by diamine oxidase, and are partially converted into the heterocyclic amines, piperidine and pyrrolidine, which are promptly excreted in the urine.[13] Our investigations have shown that in cystinuric patients, after intake of either lysine or ornithine, excretion of the heterocyclic amines is much more constant and predictable than is diaminuria. Urinary excretion of the heterocyclic amines by cystinurics is therefore analogous to the abnormal output of indolic compounds in Hartnup disease, and is similarly inhibited by sterilisation of the gut by oral neomycin.[14]

Animal experiments suggest that transport of glycine is not connected with that of any other aminoacid. Two human diseases have been described where there is an isolated renal defect of glycine reabsorption; hereditary glycinuria [15] and the acquired form of vitamin-D resistant rickets or osteomalacia.[16] The former disease is more likely to involve a specific transport defect of glycine, since the glycine clearance and urinary output of glycine is about six times as great as in vitamin-D resistance. We suggest therefore that the intestinal absorption of glycine should be investigated in the patients of the unique family reported by de Vries et al.[15] If defective glycine absorption is found, the three hereditary diseases cystinuria, Hartnup disease, and hereditary glycinuria will be proved to be specific disorders of aminoacid transport, each involving the three groups of aminoacids which show mutual competition for separate transport systems in the dog's kidney. We think the current evidence is sufficient to describe these three diseases together, and are pleased to note that they are discussed in successive chapters in the recent monograph *The Metabolic Basis of Inherited Disease*.[4]

Prediction of other diseases in which specific defects of both renal and jejunal transport systems are likely to occur is more difficult. One possible veterinary condition is the specific defect of uric-acid transport known to occur in the kidney of the Dalmatian coach-hound.[17] Again, transport of purines by the intestine of this species has not been investigated to date.

Finally, we should like to acknowledge that our recent investigations of transport defects in Hartnup disease and in cystinuria are merely a simple and logical extension of the classical researches of Dent and his colleagues [7 18] of the renal disorder in these two conditions. In addition our work would have been impossible without the continued cooperation, encouragement, and advice of Professor C. E. Dent.

M. D. MILNE
A. ASATOOR
L. W. LOUGHBRIDGE.

London, W.12.

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8. Milne, M. D., Asatoor, A., Edwards, K. D. G., Loughridge, L. W. (in preparation).
9. Von Udransky, L., Baumann, E. *Z. physiol. Chem.* 1889, **13**, 562.
10. Garrod, A. E. *Lancet*, 1908, ii, 1, 73, 142, 214.
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13. Von Euler, U. S. *Acta pharm. tox. Kbh.* 1940, **1**, 29.
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16. Cusworth, D. C., Dent, C. E. *Biochem. J.* 1960, **74**, 550.
17. Friedman, M., Byers, S. O. *J. biol. Chem.* 1948, **175**, 127.
18. Baron, D. N., Dent, C. E., Harris, H., Hart, E. W., Jepson, J. B. *Lancet* 1956, ii, 421.

IS RADIOLOGICAL EXAMINATION OF A TWISTED ANKLE NECESSARY?

SIR,—Dr. Garfield's study (Nov. 26) is a laudable attempt to rationalise the casualty officer's approach to the twisted ankle. Such re-appraisals of physical signs in relation to radiological findings are indeed necessary, but many of Dr. Garfield's conclusions are open to serious criticism.

It would be quite wrong to draw conclusions about the physical signs in major fractures based on a series including only 8 such injuries, but I would wholeheartedly agree that the physical signs alone are an unreliable guide to the nature of underlying soft-tissue and bony injuries, and this was my own experience in a critical survey I carried out on 130 sprained ankles some years ago. Dr. de Kretser must be right in emphasising the time factor in relation to the appearance of both bruising and swelling. No-one will disagree with Dr. Garfield that the patient who has neither moderate tenderness, bruising, or swelling need not generally be referred to a casualty department for diagnosis or treatment.

May I emphasise that it is because careful correlation between physical signs and underlying damage has generally failed to provide an accurate assessment of underlying soft-tissue damage that radiological examination is imperative where there is significant swelling, bruising, and tenderness. Dr. Garfield has indicated that it is impossible to take radiographs of the ankle in inversion in a busy casualty department and he has dispensed with this method of assessment. If he continues to neglect this all-important procedure he will find an increasing number of patients in whom the "healthy" side shows a greater tilt than the injured, simply because it has been injured previously and not recognised, or inadequately treated.

"Radiological control is the basis of all good treatment of sprains."

Chirk,
near Wrexham. J. ROWLAND HUGHES.

SIR,—The method of ankle strapping recommended by Mr. Schraibman (Dec. 17) is ingenious, but not new. He will find an excellent description of stirrup strapping for ankle sprains in *Illustrations of Surgical Treatment* by E. L. Farquharson, published in 1939.

Amersham General Hospital
Amersham,
Bucks. H. D. W. POWELL.

SHORTAGE OF RADIOGRAPHERS

SIR,—I was glad to see in your leading article of Dec. 10 the comment: "It is certainly going to be hard to supply enough well-trained radiographers to staff fully every X-ray department in the country. And if, as seems very likely, it is impossible without a big increase in their salaries, the money must be provided."

Most radiologists have felt for many years that one of the most important factors in the chronic shortage of radiographers has been inadequate remuneration. This has already done considerable harm in handicapping recruitment and causing loss of radiographers from the service.

In a recent meeting of the Wessex Association of Radiologists, there was unanimous agreement that considerable increase in salary of the superintendents and senior radiographers was urgently needed. Many senior staff have for years continued in their chosen life's work in spite of the discouraging conditions of service. The smooth running of an X-ray department and the quality of work produced largely depend on them, and it is becoming increasingly hard to find candidates of the right type.

Now that the Adrian Committee have made their report I hope that pressure will be brought upon the Ministry, from as many sources as possible, to act without further procrastination.

X-ray Department,
Royal Isle of Wight County Hospital,
Ryde. W. R. R. THURSFIELD.

GONADAL DYSGENESIS (TURNER'S SYNDROME) WITH MALE PHENOTYPE AND XO CHROMOSOMAL CONSTITUTION

SIR,—The case of this condition reported by Dr. Bloise and his colleagues [1] is sufficiently unlike other cases of XO karyotype to raise the question of whether the reduction to 45 chromosomes has resulted from reciprocal translocation between X and Y, with loss of a small centric fragment of Y. Such a translocation could well yield a chromosome that would fit into the 6–12 group and would be expected to yield genitalia of the type displayed by the patient.

Department of Anatomy,
The Medical School,
Newcastle upon Tyne. JOHN GRAY.

SMOKING AND SCHOOLCHILDREN

SIR,—In his report on the attitude of schoolchildren to smoking, quoted in your columns on Dec. 3 (p. 1240), the health education officer of Middlesex recommends wider publicity and enforcement of the law prohibiting under-16s from purchasing cigarettes.

Let us face facts. This law has already been rendered impotent by the triumphal advent of the cigarette-vending machine, which literally any child can use. It is clear that the automatic vendor is here to stay, and enforces a frank and full reappraisal of our preventive policies. Legislation is no answer. Current law is an ass, and to propose fresh legislation (e.g., to illegalise smoking itself under a certain arbitrary age) is to court certain ridicule and make forbidden fruit sweeter still.

Are we, then, to leave our children unprotected and uninformed, at a time when we are armed with a mounting mass of evidence of the hazards to health of cigarette-smoking? Never was a rising generation exposed to grosser temptations. The wares are seductively advertised on all sides; pocket-money is invariably lavish, and the traditional forces of discipline and restraint are being steadily eroded by our pleasure-seeking society.

The gravity of the problem among schoolchildren is well recognised, yet action has been negligible. If the remedy is to be found, it is in Mr. Penn's own field. Only a concerted and urgent effort by all concerned, to decide upon and exploit the best means of propaganda, can hope to reduce the incidence of early addiction. As the report [1] of the Joint Tuberculosis Council of Great Britain concludes, "Special efforts should be made to discourage young people from taking up smoking".

Perhaps the Central and Scottish Health Services Council Joint Committee on Health Education will address itself to this problem. We need an active policy, virile publicity, and—above all—a dynamic personal effort from all the members of our profession who have so shamefully neglected their duty to put the facts before the public.

Bristol. ALEXANDER W. MACARA.

CURE OF TOBACCO ADDICTION

SIR,—In recent issues of your journal there are discussions about smoking in children and adults. Perhaps it would interest your readers to know that in Stockholm, at the University Medical Clinic at the Karolinska Hospital, we have done some research into how to stop smoking.

Our experience now includes about 4000 smokers, who all wished to stop smoking but who were unable to manage it themselves. Using a combination of knowledge, psychotherapy, and medical treatment we have had good results in 99% last year. 88% stopped entirely and another 11% decreased their cigarette consumption to a quarter or less of what it was.

Last year's results were published at the annual meeting of the Swedish Medical Association on Dec. 3. Earlier publications appeared in the *Svenska Läkartidningen* [2 3] and in the *British Columbia Medical Journal*.[4]

Department of Medicine,
Karolinska Hospital,
Stockholm. BÖRJE EJRUP.

REFRIGERATED VENTILATION FOR OPERATING-THEATRES

SIR,—I write in support of Mr. Murley's letter of Dec. 17.

Since 1947 I have operated on about 5000 patients in temperatures ranging between 47°F and 60°F and can make nothing but favourable comments on the application of cooling in operating-theatres. I claim that, as a result, these patients have lost less blood and had fewer wound and chest complications and required lesser amounts of anæsthetic agents. "Surgical shock" has been almost eliminated, and transfusions of blood and/or saline have been seldom required. Furthermore, the surgeon has been able to complete his lists in greater comfort, and at the end he and the nursing staff (who after all are working in these excessively hot and humid atmospheres all day) were very much less tired.

I hope later to publish my results of this series, but early mention of it has been forced upon me by the Ministry's reluctance to install refrigerated ventilation in our new theatre suite which is shortly to be built. The surgical staff here, like Mr. Murley at St. Albans, have warned the regional board that refrigerated ventilation should be installed. It seems a pity that the Ministry of Health bulletin on operating-theatre suites should have been published on advice given by people who are obviously out of touch with modern operating requirements, and that such eminent men as Williams, Blowers, Garrod, and Shooter should have followed the same course without seeking the advice of those of us who are familiar with the advantages of refrigerated ventilation.

Is it not time that surgeons should have a say under what conditions patients should be operated upon, and avoid leaving the decision to uninterested bodies who have not had the experience of the disasters of an overheated humid theatre

1. Bloise, W., de Assis, L. M., Bottura, C., Ferrari, I. *Lancet*, 1960, ii, 1059.

1. *Tubercle*, 1960, **41**, 301.
2. Ejrup, B. *Svenska Läkartidn.* 1956, **53**, 2634.
3. Ejrup, B. *ibid.* 1959, **56**, 1899.
4. *Brit. Columb. med. J.* July, 1960.

atmosphere? So convinced am I of the benefits of refrigeration in the theatre that I have offered to install at my own expense a refrigerating plant if the Ministry be short-sighted enough to omit it in our new block—and it won't cost the £5000 they talk about.

I hope that other surgeons, like Mr. Murley, will come forward in support of refrigerated ventilation, and I know they will do so once they have experienced the great benefits of such a system. Mr. Enoch Powell has stated at the Conservative Conference when referring to hospital building "that what was done today should be fully in line with the most modern medical knowledge and practice and take account of future trends". The late war will have been fought in vain if patients in 1961 are allowed to be heated during or after operation.

Doncaster. DAVID AIKEN.

SIR,—We read Mr. Murley's letter with interest. We have for long held the same views and regret the decision of the Ministry not to supply this type of ventilation in their new theatres, with the exception of neurosurgical theatres.

Having worked in new theatres with unrefrigerated air-conditioning, we would support Mr. Murley's statement that the temperature does not come down to a satisfactory level and there is a risk that the patients will become overheated, particularly since they are usually covered by towels and can lose heat in very limited areas.

Secondly, the theatre staff are not working in the comfort they should be able to, and particularly the surgeon, who is subject to mental and physical strain. After any long operation it is not infrequent for the surgeon to have to change his operating clothes.

One would hope that in the new theatres being built conditions under which the sweat dripped from the surgeon's brow into the patient's wound would become a thing of the past. In this area two new theatre blocks are being built, and though excellent in most respects they lack the advantages of full air-conditioning.

G. P. ARDEN
Windsor. R. H. MAUDSLEY.

CHEMOPROPHYLAXIS IN CHRONIC BRONCHITIS

SIR,—But at least Dr. Winston's battered Battersea bronchitic (Dec. 24) has, thanks to 'Omnimycin', done a day's work, though probably whilst waiting in his wet bus queue envying Grandma's need for her daily purge.

London, S.W.1. BENJAMIN LEE.

HYSTERECTOMY AND BILATERAL OOPHORECTOMY

SIR,—I hope your annotation of Oct. 22 and Professor Nixon's letter of Oct. 29 will be noted by those gynæcologists who extirpate normal ovaries when performing hysterectomy in premenopausal women.

May I cite my own case? At age 40, after hysterectomy for fibroids I found that both my normal ovaries had been removed. No intimation was given me by the surgeon before operation that this was his intention, and I discovered the fact only on reading my pathological report. This practice, performed to prevent an incidence of cancer of the ovary of the order of 1 or 2 in 5000,[1] may result in the development of early and severe atherosclerosis in a much larger proportion of women, if the findings of Oliver and Boyd [2] and others are the general result. In addition, as Professor Nixon so rightly states, the severe psychological effects of such an operation performed on women still comparatively young should be considered. Is this not an example of limited specialisation, when the ovary is treated as a pelvic organ and forgotten as an endocrine gland?

What indeed are the long-term effects of early castration in women? Do many thus treated achieve old age? Can the surgeons who perform this operation answer this question? I would challenge them to do so and ask also what steps in follow-up and prevention they propose for this group of women now made so much more vulnerable to arterial disease. Oliver suggests that all such women should receive œstrogen therapy, and the question arises whether, in women who have been castrated by the gynæcologists, the cardiologists should institute œstrogen or other therapy, in an endeavour to prevent coronary or other arterial disease.

A WOMAN DOCTOR.

1. Jeffcoate, T. N. A. Principles of Gynæcology; p. 667. London, 1957. Schabort, J. W. *Trans. Coll. Physns Surgns Gynæcts, S. Afr.* 1960, **4**, 11.
2. Oliver, M. F., Boyd, G. S. *Lancet*, 1959, ii, 690.

DICHLORPHENAMIDE FOR RESPIRATORY INSUFFICIENCY

SIR,—The encouraging report on the use of dichlorphenamide for respiratory insufficiency by Naimark et al.,[1] summarised in an annotation,[2] must have stimulated many workers to use this drug for respiratory insufficiency in emphysema. Emphysematous patients with persistent and appreciable hypercapnia (above 55 mm. Hg), however, are not common and for this reason and because the drug holds promise, I should like to record its use in 7 patients.

4 patients with a pCO_2 persistently over 60 mm. Hg were moderately desaturated and slightly acidotic. 2 patients had a pCO_2 of between 50 and 55 and were slightly desaturated but fully compensated. 1 patient had a normal pCO_2. All were treated when in a steady state and the dose of dichlorphenamide was 50 mg. four times daily.

3 had to stop treatment because of severe headaches and 1 because of severe and intolerable pins-and-needles in the fingertips. 1 patient persisted with the treatment in spite of the headache and later developed a "dopey" feeling, anorexia, and pain in the legs. Another patient continued the treatment in spite of headaches which lasted half an hour after each dose because he said that he was "so much better it was worth it". His F.E.V.$_1$ and F.V.C. almost doubled. It is only right to point out, however, that he felt as well when off tablets for one month and his F.E.V.$_1$ and F.V.C. fell only slightly. The toxic effects could come on after taking only 100 mg. of the drug. The therapeutic effects would seem to last for three to four weeks after stopping treatment.

In general the F.E.V.$_1$ rose by up to 25% and the pCO_2 fell by 5–15 mm. Hg. In 2 cases when it was measured the oxygen saturation rose by 6% and 10% respectively. The arterial blood pH fell by about 0·11 but later returned to its previous level.

2 of the patients with pCO_2 over 60 also had chronic heart-failure resistant to digoxin and to mercurials alone or in combination with aminophylline and spironolactone. Dichlorphenamide caused diuresis after five days' treatment in 1 but not in the other. Sodium and chloride excretion was increased but that of potassium was unchanged. The unresponsive patient needed acupuncture of the legs which resulted in a dramatic and sustained improvement.

It is admittedly difficult to assess the value of a drug in emphysema, the clinical state of which can vary so rapidly and unexpectedly, and where there is a good chance of any new drug being well received by the patient. But the subjective improvement in the treated patients was so striking that I am sure that dichlorphenamide should be given an extended trial in the emphysematous patient with CO_2 retention. It seems

1. Naimark, A., Brodovsky, D. M., Cherniack, R. M. *Amer. J. Med.* 1960, **28**, 368.
2. *Lancet*, 1960, i, 1120.

incredible that Naimark et al. encountered severe headache only once in treating 15 patients with 200 mg. a day. My experience is that it is preferable to start with one (50 mg.) tablet a day and increase if possible to four.

Chase Farm Hospital,
Enfield,
Middlesex. THOMAS SIMPSON.

COST OF THE HOSPITAL SERVICE

SIR,—Dr. Terry (Dec. 24) should accept with more caution what he reads in the daily newspapers. The belief that there has been an " alarming rise in the cost of the Hospital Service ", though widely accepted, is false. In the last decade cash expenditure on the hospitals has risen steadily, but meanwhile the share of the nation's resources going to them has in fact declined slightly. As the nation has become more prosperous, the hospitals have lagged behind. Where is the rise, and what is alarming about it?

The use of funds by hospitals in Britain is undoubtedly inefficient. To improve efficiency, however, will not make them cheaper—it will make them better hospitals. Similarly, the suggestions put forward by Dr. Terry in his letter would not reduce the cost of hospitals—they would improve the quality of general practice.

Richmond,
Surrey. J. R. SEALE.

BLOOD-CHOLESTEROL AND ASPIRIN

SIR,—The effect of salicylates on cholesterol is mentioned in Savill's *System of Clinical Medicine* (13th ed., 1950): " Sodium salicylate . . . increases the excretion of bile salts and cholesterol " and it is claimed that this is related to work by Schmidt et al. in 1938.[1]

Would increased excretion of cholesterol be accompanied by increased speed of turnover of steroids, so that this explains the similarity of effect of salicylates and steroids in rheumatism? Salicylates are excreted as conjugates with glucuronic acid in the urine and the reduction of cholesterol may be related to the increased production of glucuronic acid.

Since the communication by Dr. Eidlitz (Nov. 19), a male senior technician (A) and I (B) have taken 5 tablets of aspirin daily for 2 weeks (gr. 25 daily). Results:

Serum-cholesterol (mg. per 100 ml.)	*Original level*	*1st week*	*2nd week*
A	190	205	185
B	250	235	205

We use a method of estimation which is reproducible to 10%, using a modification of Rosenthal's colour reagent as described by Leffler.[2] The level of cholesterol in my serum has been 250 mg. per 100 ml. regularly and has been used as a check on laboratory accuracy together with a ' Chemtrol ' standard.

Previously, we had tested the effect of ascorbic acid 500 mg. per day for 10 days on eight normal and two abnormal people (three males and seven females). Ascorbic acid is highly unsaturated and contains three double bonds. In this small series (cholesterol values between 330 and 150 mg. per 100 ml.) there was no marked difference, except in my case where the post-test level dropped to 210 from an original 250 mg. per 100 ml. In four of the females there was a drop of 20 mg. per 100 ml.

Perhaps salicylates may be of benefit in preventing gallbladder dysfunction, especially in pregnancy. The few tests I have done so far seem to indicate that the cholesterol levels are more easily influenced in females than males, and it would be interesting to know the sex in the series described by Dr. Eidlitz.

Chichester. PHYLLIS DAGNALL.

1. *Amer. J. dig. Dis.* 1938, **5**, 613.
2. Leffler, H. H. *Amer. J. clin. Path.* 1959, **31**, 310.

PROTEIN-LOSING ENTEROPATHY IN THE SPRUE SYNDROME

SIR,—The paper by Dr. Parkins (Dec. 24) is of great interest because it serves further to lengthen the list of gastrointestinal conditions in which internal plasma-protein loss may occur. To his series of 11 cases may be added that of a 39-year-old woman, observed at the National Institutes of Health, suffering from gluten-sensitive enteropathy.

She had a serum-albumin level of 2·2 g. per 100 ml., and excreted 3·4% of a test dose of ^{131}I-polyvinylpyrrolidone (P.V.P.) in the fæces. Because of the appearance of her jejunal biopsy, a gluten-free diet was prescribed. Follow-up information obtained through her own physician, Dr. Hershel Jick, reveals that her symptoms have been relieved, and a serum sample which he provided yielded an albumin value of 3·5 g. per 100 ml. This is a low normal value by the method employed here.[1]

It is not sufficiently appreciated that successive batches of P.V.P., due to differences in molecular-weight distribution, may vary considerably with respect to their persistence in the blood, and to the rates of their urinary and fæcal excretion. Valuable data on the biological behaviour of P.V.P. as a function of molecular weight are given by Ravin et al.[2]

Dr. Parkins noted that none of his 10 normal subjects excreted more than 1% of an intravenous dose of ^{131}I-P.V.P. in the fæces. This finding agrees exactly with my own experience with the preparation which he was using. The supply of polymer used for the preparation of ^{131}I-P.V.P. for my initial studies [1] having been exhausted, it was necessary late in 1959 to prepare a new batch, and it was this material which was provided for Dr. Parkins' use. Thus it is necessary to consider his case 2 to have yielded an abnormal result on the P.V.P. test. I am concerned about his case 9, however, since the P.V.P. excretion seems unduly high, especially in the face of a high serum-albumin level. One wonders whether this patient, a baby girl, might not have succeeded in contaminating the fæcal samples with some radioactive urine.

Finally, a comment on his failure to find a correlation between P.V.P. excretion and serum-albumin levels seems appropriate. Since the sprue syndrome may show spontaneous fluctuations in severity, it may be that the intestinal protein loss associated with it is an intermittent, and not a constant, process. If so, the serum-albumin level should reflect the balance between synthesis and degradation or loss, averaged over a period of many days. The P.V.P. test, on the other hand, serves as an index of the protein loss on the day of the injection. The rapid disappearance of P.V.P. from the blood [2] would lead one to expect this relationship, and it is borne out by our experience with 2 patients with abnormal P.V.P. excretion and diarrhœa. In each of these, stools were counted on a daily basis, with the result that more than 70% of the total fæcal output was accomplished on the first day. Thus, with a disease causing intermittent internal plasma-protein loss, the results of repeated P.V.P. tests should be expected to vary widely, and their correlation with serum-albumin levels might be very poor, even if additional factors such as malnutrition and impaired protein synthesis did not enter into consideration.

It is my present belief that a single P.V.P. test cannot be used to quantify the severity of internal plasma-protein loss in a given patient. The most important limiting factors are the heterogeneity of the polymer, the fact that its distribution and excretion in vivo do not correspond exactly to those of the plasma-proteins, and the possibility of fluctuations in the severity of the protein loss. It is possible, however, to arrive at a rough, empirical correlation between serum-albumin levels and the results of the P.V.P. test when one surveys a group of patients all of

1. Gordon, R. S., Jr. *Lancet*, 1959, i, 325.
2. Ravin, H. A., Seligman, A. M., Fine, J. *New Engl. J. Med.* 1952, **247**, 921.

whom have been tested with the same preparation of P.V.P. The test can then be used to indicate qualitatively the presence of an internal protein leak, and to serve as an index of its momentary severity. This correlation curve must, however, be established anew with each fresh P.V.P. preparation. It is therefore greatly to be hoped that those who propose to prepare ^{131}I-P.V.P. for future clinical use will make every effort to standardise their materials and avoid unnecessarily frequent changes.

National Heart Institute, Bethesda, Maryland. ROBERT S. GORDON.

TREATMENT OF DRUG ADDICTION

SIR,—I congratulate Lady Frankau and Dr. Stanwell (Dec. 24) on a remarkable therapeutic feat in successfully treating 32 out of 51 drug addicts between August, 1958, and March, 1960. Their results have never been remotely approximated by any other workers in this most unrewarding of psychiatric fields. In view of this success it is to be hoped that Lady Frankau will follow-up the 32 patients who, at the time the article was written, were believed to be no longer dependent on drugs.

It would be interesting to know how many of the patients relapsed in the few months after withdrawal, because unfortunately 9 cases out of 10 relapse within, roughly, six months.

If a substantial proportion of their patients are still free of addiction I hope that Lady Frankau and Dr. Stanwell will indicate to what particular aspects of treatment they attribute their success, for I could not find in their report reference to any techniques or therapy which have not already been adequately practised with conspicuous failure by other doctors.

It is not difficult to take patients off drugs but it is quite another proposition to ensure them against relapse.

The only incentives of drug addicts to seek treatment, in my experience, are those negative ones mentioned by Lady Frankau and Dr. Stanwell—namely, difficulties with the authorities, or domestic or financial problems—and this faulty approach probably accounts for the very high proportion of failures. On the other hand, relapse can invariably be anticipated even in addicts with powerful positive motives for cure. Even intensive psychotherapy before, during, and after treatment fails to relieve the frustration and monotony of consistent therapeutic failure.

The only effective means of combating relapse is by rehabilitation in a new environment, a most difficult process.

Lady Frankau was surely singularly fortunate in that so many of her patients could afford nursing-home treatment. My experience, in over thirty years, has been very different, only about 5% of cases having been able to meet the quite modest fees required and then only by either borrowing from or having them provided by some good Samaritan or some less worthy person sexually interested in the patient.

My cases, like Lady Frankau's, have fallen into one of three main groups. In group 1 are the most stable and worthwhile types, many of them professional people who seek treatment in much the same circumstances as alcoholics. In group 2 are well-educated, often financially independent, æsthetic, weak-willed, self-indulged, and hysterical characters who pay lip service only to treatment, and who will only enter a nursing-home provided they believe that some of their drug will be forthcoming if they cannot " tolerate " its withdrawal. Very few of them are ever cured. Group 3 comprises low-grade night-club hostesses, prostitutes, ponces, sexual perverts, drug pedlars, and a certain proportion of people associated with the world of entertainment. They rarely have any incentive to attempt a cure and are mostly immature psychopaths who lead degraded lives and die often by accident, from chronic alcoholism or suicide. Cure is rarely possible outside prison.

Most addicts on presenting themselves for the first time state that they have obtained drugs illicitly. They express the desire to be cured but assert that they will not have the necessary funds for a few weeks. They ask for a daily supply of drug far in excess of their requirements. No drugs should be prescribed until they have been kept under observation for sufficient time to provide an opportunity for the assessment of the severity of deprivation symptoms. The amount of drug required to relieve their distress and the duration of relief will help one to determine how much should be prescribed. Otherwise the amount of drug provided is a matter of pure guesswork based on the plausible prevarications of resourceful and determined addicts motivated by fears of deprivation and consequently anxious to obtain as much as possible. Further, the distribution of drugs based on the addicts' estimation of their requirements places the doctor in the unenviable position of a professional pedlar.

Treatment is invariably postponed for months unless the practitioner makes it quite clear that he will prescribe drugs for a limited period only after which the patient must be prepared to enter an institution or nursing-home. This interregnum can be used to study the patient's personality, complexes, and conflicts, &c., with a view to his ultimate redemption. Very explicit conditions should be laid down at the start of treatment or when first authorising a supply of drug. It is one of the few professional relationships in which an uncompromising and unrelenting attitude must be adopted as being in the best interests of the patient.

In referring to cases which fall into their group 2, Lady Frankau and Dr. Stanwell state that " the energy and concentration which should have been devoted to making a success of a profession or business were directed to the pursuit of drugs, which alone could provide *relaxation*, a *sense of security*, and *freedom from anxiety* ". I regard this as a most misleading statement because, apart from the soothing and pain-relieving effects of dangerous drugs when administered for normal therapeutic purposes, they can produce only the most transient relief of insufferable deprivation symptoms in cases of addiction.

It seems that Lady Frankau and Dr. Stanwell do not necessarily equate " clear of dependence on drugs " with *cure of addiction* otherwise one might have expected to find the latter term mentioned in the context of their article. There is, of course, a very definite distinction. " Clear of dependence on drugs " may indicate a purely temporary state of affairs, while *cure* suggests permanent emancipation from dependence on drugs. If they do not equate the two terms, my congratulations on their results must be modified and the value of their contribution reconsidered.

London, W.1. ELLIS STUNGO.

HÆMODIALYSIS COMBINED WITH ULTRAFILTRATION

SIR,—Dr. Ritchie and his colleagues (Dec. 10) stress the advantages of the Kolff twin-coil artificial kidney in hæmodialysis combined with ultrafiltration. Although we agree with the authors that effective ultrafiltration with a perfusion speed optimal for dialysis seems more possible with this type of kidney, we still think that the Alwall kidney has the advantage of controllable (and not obligatory) ultrafiltration. We think that the Skeggs-Leonard type of artificial kidney and especially the modification devised by Kiil (Oslo) [1] will finally satisfy the requirements of an ideal artificial kidney of small extracorporeal blood-volume, high dialysis capacity, controllable ultrafiltration, and independence between ultrafiltration and perfusion speed. At this moment our efforts are directed to the construction of such a parallel-flow kidney, in many ways similar to the type devised by Kiil.

E. E. TWISS
Rotterdam. M. M. P. PAULSSEN.

1. Kiil, F. *Acta chir. scand.* 1960, suppl. 253, p. 142.

PREVENTIVE GERIATRICS

SIR,—I should like to congratulate Dr. Duncan Macmillan (Dec. 31) on his bold approach to the prevention of mental ill health. He rightly emphasises the part played by family rejection in the development of senile psychosis, but I rather regret that he does not refer to community rejection which often plays a very similar part which is sometimes even more important.

In our social life today there is little place for the ageing and this leads to mental misery and breakdown.

I was disappointed therefore that he did not allude to the sheltered workshops which provide remunerative employment, such as that pioneered in Finsbury, and those that have now developed in many centres, and which have preserved the mental health and wellbeing of many elderly by enabling them to feel that they still have a place in our community life as well as in other ways.

Public Health Department,
Finsbury Health Centre,
London, E.C.1.

C. O. S. BLYTH BROOKE
Medical Officer of Health.

TREATMENT OF CARBON-MONOXIDE POISONING WITH OXYGEN UNDER PRESSURE

SIR,—We read with interest the preliminary communication from Dr. Smith and Dr. Sharp, and we should like to bring to notice a new treatment of acute carbon-monoxide poisoning, using our simple device for extra-corporeal circulation. We applied the same principles of correction of the carboxyhæmoglobin content of the blood as Smith and Sharp and diverted blood from the patient's circulation into the oxygenator of our pump by way of the femoral vein and artery. We thus achieved a rapid correction of the anoxia and relieved the acute carbon-monoxide poisioning.

Prague,
Košice,
Czechoslovakia.

J. POKORNÝ
S. SIMKO.

Medicine and the Law

The Duty of a Psychiatrist

A PSYCHIATRIST giving evidence in a criminal case is offering his expert opinion on the state of mind of the accused person. He must first ascertain the facts and then form an opinion on them. The task of assembling the facts is always a responsibility and may be troublesome. The expert must give due weight to all the facts and overcome the subconscious temptation to ignore or underestimate the significance of inconvenient facts. Opinions must fit facts, not facts opinions. He must also be satisfied as to the reliability of the facts in question; and in psychiatry the principal source of information will often be the person under consideration—that is, in a criminal case, the accused himself.

A reminder of these responsibilities came recently from Lord Wheatley in the course of a criminal trial in the High Court at Edinburgh.[1]

The accused was charged with indecent practices with nine youths between June, 1956, and October, 1960. Counsel for the defence had quoted from a medical report submitted by a psychiatrist who had examined the accused. In the report it was alleged that the youths concerned were already corrupted when they met the accused. This appears to have been challenged by the prosecution, and counsel for the defence conceded that the opinion formed by the psychiatrist had been based on information given by the accused.

Commenting on this, the judge said: "We frequently get reports from psychiatrists in cases of this nature when an opinion is expressed purely on the history presented by the accused himself. Such a history may be true or false; or it may be partly true and partly false; and it may be highly coloured. But if any doctor is going to tender an opinion for the benefit of the court, then it seems to me that it is only elementary that the doctor should make some endeavour in order to satisfy himself that the facts on which it is presented are well founded."

1. *Scotsman*, Dec. 24, 1960.

Public Health

Carbon-tetrachloride Fire-extinguishers

IN spite of all that has been written about the need for care when carbon-tetrachloride (C.T.C.) fire-extinguishers are used either in confined spaces or in situations where the liquid comes in contact with hot metal, accidents still happen. Recently, 76 people were taken to hospital with suspected phosgene poisoning after a C.T.C. extinguisher had been used on a fishpan fire in a factory canteen in Leeds.[1] They were given oxygen and kept in hospital overnight for observation, though none of them complained of feeling ill.

C.T.C. has a narcotic effect, and people have died from inhalation of the vapour when an extinguisher has been used in an enclosed space; but individual susceptibility varies greatly. Danger arises from the decomposition of C.T.C. when it comes in contact with a hot surface. C.T.C. may break down directly into phosgene (carbonyl chloride) and hydrochloric acid, but more probably a three-stage reaction takes place. The C.T.C. dissociates into carbon and chlorine; the carbon is oxidised to carbon monoxide, which then combines with the chlorine to give phosgene. In the presence of water, C.T.C. hydrolyses to carbon dioxide and hydrochloric acid. This is unlikely to be a toxic hazard, but C.T.C. which has become damp will attack the metal of a fire-extinguisher with possible serious results, especially with pressure-type extinguishers.[2]

Under some circumstances, therefore, several toxic or irrespirable gases may be present—C.T.C. vapour, phosgene, chlorine, carbon monoxide, and carbon dioxide. The maximum permissible concentration for chronic exposure to phosgene is 1 part per million (p.p.m.), chlorine 1 p.p.m., and C.T.C. 25 p.p.m.[3]

Nevertheless, provided the hazards are remembered, C.T.C. remains one of the more useful fire-extinguishing substances. It is less toxic than the more effective methyl bromide, and is particularly suitable for fires involving electrical apparatus, though its fairly high freezing-point has disadvantages in cold climates.[4]

Infant Mortality in Glasgow

In his latest annual report the medical officer of health for Glasgow remarked that in that city the perinatal mortality (45·5 per 1000 live and still births) was higher than in any other city in Scotland or England; and he expressed disappointment that under 60% of parturient women were confined in hospital, and suggested that the proportion should be at least 75%.[5]

A different viewpoint was expressed by Dr. W. W. Fulton at a meeting on Dec. 22 of Glasgow Executive Council.[6] Dr. Fulton declared that the way to bring down the infant-mortality rate was to build, not more maternity hospitals, but more houses. Dr. J. R. Langmuir, the chairman, said that, while the city was clearing slums and building new houses, new slums were coming into existence all the time. The old commodious family houses were being split into apartments in which people were living in squalid conditions which had to be seen to be believed.

1. *Times*, Dec. 21, 1960.
2. Manual of Firemanship; pt. 1, p. 153. H.M. Stationery Office, 1951.
3. Toxic Substances in Factory Atmospheres. Safety, Health and Welfare Booklet no. 8; pp. 7, 9. H.M. Stationery Office, 1960.
4. Cameron, A. M. Chemistry in Relation to Fire Risk and Fire Extinction; p. 184. London, 1944.
5. See *Lancet*, 1960, ii, 1151.
6. *Scotsman*, Dec. 24, 1960.

Obituary

WILLIAM EDWARD MANDALL WARDILL

M.B. Durh., F.R.C.S.

William Wardill, who died at his home in Newcastle upon Tyne on Dec. 23, had worked in Newcastle as plastic surgeon to the Royal Victoria Infirmary and as surgeon in charge of prostatic surgery at the General Infirmary, and in Baghdad as professor of surgery at the Royal Medical College. These posts suitably reflected the range of his surgical interests and experience.

He was born at Gateshead, where his father was several times mayor. He was educated at Mill Hill School and spent a couple of years beginning a commercial training before he was able to persuade his family to allow him to take up medicine, but in 1913 he began his studies at the old Newcastle medical school. Despite the interruption of the war, in which he served as a surgeon probationer R.N.V.R. and later as a temporary surgeon R.N., he qualified in medicine in 1918, and took his F.R.C.S. in 1920.

Soon after he returned to Newcastle he was appointed a surgical registrar at the Royal Victoria Infirmary and in due course was appointed to the staff. He also joined the staff of the Medical School as an assistant curator of the museum, and together with Dr. Whately Davidson produced the first modern catalogue of the collection. Later he became lecturer in surgical pathology. This close association with the Medical School brought him in touch with James Whillis, then a lecturer in anatomy, and together they elucidated some of the mysteries of the pharyngeal musculature, which ultimately led Wardill to devise his operation of pharyngoplasty.

He had been interested in cleft-palate surgery from the days when he was Grey Turner's house-surgeon. The results reported at a meeting of the Royal Society of Medicine in 1926 stimulated him to investigate the problem further, and in a Hunterian lecture in 1927, and in a paper in the *British Journal of Surgery* in 1928, he showed how the pharynx of cleft-palate patients was wider than normal. He introduced the Wardill pharyngoplasty to narrow the pharynx in these cases. Later he used the Veau method of cleft-palate operation. In his Hunterian lecture of 1933 he described further improvements in his technique and suggested a classification of speech defects which is still used today with only slight modifications.

Much of this part of his work was done at Tynemouth Infirmary and the Babies Hospital, Newcastle, where he was associated with the late Sir James Spence. But Wardill remained a general surgeon with special interests in plastic surgery and urology.

He started the urology department at Newcastle General Hospital after a visit in 1937 to the Mayo Clinic with T. J. Lane, of Dublin, to see work on transurethral resection. At the outbreak of war he began the plastic and jaw unit at Shotley Bridge Hospital, where he treated civilian and Service casualties.

In 1948 he decided not to take part in the National Health Service and resigned his appointments and emigrated to Cape Town, where he farmed for two years. But he never found in South Africa a satisfactory outlet for his energy and varied skills, and he was delighted when in 1952, shortly after his return to England, he was appointed to the chair of surgery at Baghdad. He threw himself enthusiastically and strenuously into the life of his new school, and he spent six happy years in Baghdad concentrating on clinical teaching rather than on displays of surgical dexterity, in which, he said, the other surgeons were rather better than himself. Every summer, a colleague recalls, he returned to England when he would blackmail his friends for teaching material in the shape of lantern-slides, and do a little proselytising for the Baghdad treatment of burns—a development of exposure treatment as developed by A. B. Wallace. One of his last writings was a joint letter, lately published in our columns, on the use of compressed air in drying burns.

J. P., who worked with him for over twenty years, writes:

"Wardill was an excellent clinician and surgeon, an encourager of young men, a great teacher of surgery. He did not tolerate yes-men; he expected his assistants and associates to have their own views, and this enabled him to have free discussions. His criticisms could be biting but all was meant for one aim, perfection; he was not satisfied with anything less. He was continually after new ideas right up until his fatal illness. The late Sir Harold Gillies said 'Visits to Wardill at Shotley Bridge were always stimulating and produced argument'. It is difficult to realise that Wardill's stimulating discussions, friendly smile, and witty talk are no more."

J. A. C. remembers Wardill in his early Newcastle days as one of a triumvirate of which James Spence and Arthur Bernard Shaw were the other members:

"To the broad humanitarian wisdom of James Spence, and the cool scientific outlook and cultured background of Shaw, Wardill brought the catholic interests of the born naturalist and an active, inquiring, and creative mind. Much of his best work in child surgery, pathology, and cancer research was done in close consultation with either Spence or Shaw, and these years of his friendly and intellectual fellowship with them were perhaps the happiest of his life.

"Wardill's range of interests and talents was extraordinary. From his schooldays he had been a keen field naturalist, with a special bent towards marine biology. He was a competent musician and an accomplished metal worker, and in Baghdad he added archæology to his interests. There were few scientific subjects on which he could not talk with intelligent and lively understanding. He wrote comparatively little, though his published papers were important; but as a conversationalist he excelled, and he could talk for hours with an amazing command of vivid imagery and pertinent and at times pungent language and wit. It was this gift of communication by the spoken word which made him an outstanding teacher both in the museum and by the bedside. His museum classes in Newcastle came to be recognised as an essential part of the education of every final-year student, and were invariably crowded to overflowing.

"Inevitably Wardill became involved in the increasing claims of hospital and private practice. Here again his interests were wide-ranging. He would develop at considerable pains some particular surgical technique—Ramstedt's operation, pharyngoplasty, plastic surgery, the surgery of the rectum, and then move on to something else. His final excursion along these lines was into prostatic surgery. After anatomical studies, and some exploration of a completely new method of attack upon the problem of prostatic enlargement, he decided to take up punch prostatectomy, and proceeded to qualify himself by spending, on two separate occasions, a lengthy period at the Mayo Clinic.

"He was a northerner of northerners, independent, blunt, resolute to the point of obstinacy at times, but he had the saving gift of humour and a charm of manner when he felt at ease and in understanding company, which made him a delightful companion. His talents were unhappily never given full scope or opportunity to fructify as abundantly as they might have done. Only by a hair's breadth did he fall short of being one of the outstanding surgeons and teachers of his generation, but his achievements, nevertheless, were such as many a man might envy".

Mr. Wardill married Mary Russell Campbell, M.B., who died in 1942. In 1951 he married again, and his second wife survives him with three sons and three daughters of his first marriage.

MARK OLIVER HUNTER

M.A. Cantab., M.R.C.S.

THOUGH Dr. M. O. Hunter retired from his practice at Haywards Heath in 1947, his patients and his colleagues still remember his humanity and devotion.

He was born at Esher and was educated at Winchester and Trinity College, Cambridge. He entered a solicitor's office with the intention of becoming a partner in the family firm, but he soon abandoned the law for medicine, and he qualified from St. George's Hospital in 1905. After holding house-appointments in London at the Royal Hospital for Diseases of the Chest and at the Evelina Hospital for Children he joined a general practice in the Isle of Wight in 1906. A few years later he moved to Hatch End. During the 1914–18 war he served in the Navy as a temporary surgeon. In 1919 he returned to his practice, but soon afterwards he became a medical officer to the Ministry of Pensions and chairman of the officers court of the Pensions Appeal Tribunal.

In 1924 he returned to general practice and settled in Haywards Heath, where he remained till he retired shortly before the introduction of the National Health Service. F. H. M., who was on the staff of the Haywards Heath Hospital with him, writes:

"Dr. Hunter's kind and gentle manner endeared him both to his patients and his friends on the staff. He was always ready to give advice to medical men and many of us missed him when he retired. He really was the finest type of family doctor and would do everything he could for the benefit of both his patients and his medical friends."

Dr. Hunter, who died on Sept. 23 at the age of 87, was a widower. He leaves a daughter and a son, Dr. Alastair Hunter, F.R.C.P., who is dean of his father's old medical school.

ROBERT CHARLES ALPHONSE PIERRET

M.D. Paris and Lyons, F.R.C.P.

As a former director-general of the Office International d'Hygiène Publique, Dr. Pierret had met many doctors from all parts of the Commonwealth and he numbered many English people among his patients in his consulting practice at La Bourboule. As a result he had an unusual number of formal and informal links with Britain and British medicine. In 1939 he was elected to the fellowship of the Royal College of Physicians of London, and he was also an honorary Fellow of the Royal Society of Medicine and of the Hunterian Society, and a member of the Athenæum.

His father was a professor of medicine at Lyons and his English mother was the sister of Sir Armand Ruffer, the first director of the Lister Institute. He himself studied medicine in Paris, and after working in Paris hospitals he became a chef de clinique in the Faculté de Médecine. He was especially interested in diseases of the respiratory system, and in due course he built up a large consulting practice at La Bourboule where he gave especial attention to the treatment of asthmatic children. He was only able to practise as a clinician at La Bourboule during the summer, but at other times his interest in public health and hygiene occupied him as administrator, writer, speaker, and organiser of exhibitions. He was appointed director-general of the Office International in 1938, and during the German occupation he remained at his post. He succeeded in sending useful epidemiological intelligence and reports to the Allies, and on the entry of the Americans to Paris he received the thanks of the Chief of Staff of the U.S. Medical Service: he was created a commander of the Legion of Honour by the French Government.

After the war Dr. Pierret continued his work as director until the Office International was absorbed by the World Health Organisation in 1947. In 1951 he was one of a party of French professors who came to this country on a study visit at the invitation of the British Council.

N. M. G. writes:

"That Robert Pierret distinguished himself in two quite discrete fields of medicine was due to the official rule that doctors in France who practise in spas may not practise elsewhere when the season at the spas is over. Having built up a large practice at La Bourboule in the Massif Central, chiefly among children with respiratory troubles, he was invited one winter by Surgeon-General Hugh Cumming, the United States delegate to the Office International d'Hygiène Publique, to be his interpreter and personal assistant.

But Pierret's impressive presence, together with his acute mind and great financial ability, rapidly made him a personality in his own right."

Diary of the Week

JAN. 8 TO 14

Monday, 9th

INSTITUTE OF NEUROLOGY, Queen Square, W.C.1
5.30 P.M. Dr. Hugh Garland: Neurological Syndromes in the Arm.

Tuesday, 10th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.1
5 P.M. Dr. Louis Forman: Reaction of the Skin to Certain Metals. (Watson Smith lecture.)
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. *Psychiatry*. Prof. L. S. Penrose, Prof. Paul Polani: Implications of Recent Genetic Research for Psychiatry.

Wednesday, 11th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
2 P.M. Dr. D. G. Penington: Erythropoietin.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. Henry Haber: Lymphocytic Infiltrations of the Skin.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Sir Russell Brock: Views and Experiences in Surgery of the Great Vessels.
ROYAL FACULTY OF PHYSICIANS AND SURGEONS, 242, St. Vincent Street, Glasgow, C.2
5 P.M. Prof. M. L. Rosenheim: Chronic Pyelonephritis. (Walker lecture.)

Thursday, 12th

ROYAL COLLEGE OF PHYSICIANS OF LONDON
5 P.M. Dr. Clifford Hoyle: Prognosis of Pulmonary Sarcoidosis. (Marc Daniels lecture.)
ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Mr. F. G. Ellis: Ætiology and Treatment of Achalasia of the Cardia. (Hunterian lecture.)
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Mr. C. E. Drew: Observations on the Use of Profound Hypothermia in Surgery.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. M. Meara: Fungous Infections.
ALFRED ADLER MEDICAL SOCIETY
8 P.M. (11, Chandos Street, W.1.) Dr. E. R. Perth: Philosophy and Psychotherapy.

Friday, 13th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Dr. Mary McGeown: Ætiological Factors in Calculous Disease.
4 P.M. Dr. R. E. Bonham-Carter: Results of Cardiac Surgery under One Year of Age.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
5.30 P.M. Mr. Maxwell Ellis: Nasal Physiology and Pathology.
UNIVERSITY OF LIVERPOOL
5.15 P.M. (New Medical School, Liverpool.) Dr. Th. Ehrenpreis (Stockholm): Ulcerative Colitis in Childhood.

Appointments

CRAWFORD, A. S., M.D. Edin., F.F.A. R.C.S., D.A., D.P.M.: consultant anæsthetist, Royal Infirmary, Edinburgh, and Roodlands General Hospital, Haddington.

FRAIN-BELL, WILLIAM, M.D. St. And., M.R.C.P.E.: senior consultant dermatologist based at Dundee Royal Infirmary.

HUNTER, R. A., M.D. Lond., M.R.C.P., D.P.M.: consultant assistant physician, department of psychological medicine, National Hospital, Queen Square, London.

RHANEY, KENNETH, M.B. Edin., F.R.C.P.E.: consultant assistant pathologist based at Dundee Royal Infirmary and Maryfield Hospital.

TAYLOR, J. C., M.B. Lond., F.R.C.S.: part-time consultant neurosurgeon, Derbyshire Royal Infirmary, Derby.

WILSON, W. J., F.F.A. R.C.S.: part-time consultant anæsthetist, Worksop and Retford group of hospitals and Montagu Hospital, Mexborough.

Wessex Regional Hospital Board:

MURPHY, J. F. D., M.D. Dubl., D.P.M.: consultant in child psychiatry to the regional adolescent unit, Chandlers Ford.

PENMAN, W. A., M.B. Edin., M.R.C.P.: consultant physician (geriatrics), Isle of Wight group of hospitals.

STIRRAT, JEANNIE E., M.B. Birm.: part-time consultant child psychiatrist, Bournemouth area hospitals; consultant psychiatrist to the child-guidance service, Bournemouth.

Notes and News

INSTITUTE FOR SOCIAL WORK

THE successful Trust, like the successful doctor, must be sensitive to need, and the Nuffield Trust have once more shown that they can act on a timely hint with dispatch and generosity. When the Younghusband Working Party suggested that an experimental national staff college for social work might be a suitable and valuable project for a charitable trust, the Trust without delay convened a meeting of experts; and for the past year an informal working party, under the chairmanship of Mr. Farrer-Brown, director of the Trust, have been considering practical plans. These have now advanced so far that in their latest report [1] the Trust announce that they are provisionally setting aside some £250,000 for this purpose. In this enterprise they will be partnered by the Joseph Rowntree Memorial Trust who are also setting aside substantial sums.

A good deal of money will clearly be needed, for both Trusts realise that they must be prepared to finance an experiment of this kind for at least its first ten years. Though the venture is still only an item on an agenda, its sponsors have already some ideas about its future. They would prefer to base it on one of the "historic institutions which has been concerned with social work" (though they are prepared if need be to set up an entirely new institute), and talks are at present in progress. They hope, like the Younghusband Working Party, that the institute will become a focal point for all aspects of experiments in training and methods, and for research. It is expected to need a minimum full-time staff of a principal, three lecturers, and one specialist in research.

During the year the Nuffield Trust had an income of £1,850,000, an increase of £475,000 over the previous year. Their tendency has been to make larger grants than in the past. Besides the allocation for the proposed institute, they have made the following awards, many of which have already been announced: £62,500 to the Postgraduate Medical School of London for a unit of clinical physiology; £100,000 to the Zoological Society of London for an institute of comparative medicine; £60,000 (since increased to £100,000) to the Royal National Throat, Nose and Ear Hospital, London, for a hearing and speech centre; £250,000 to the University College of Rhodesia and Nyasaland for a new medical school; and £25,000 over five years to the United Oxford Hospitals for research in the department of neurology of the Radcliffe Infirmary under Dr. Ritchie Russell.

OXFORD HOSPITALS AND CENTRES

IT seems that a modern hospital, to keep alive, must grow; and this is being illustrated by the medical centres in Oxford. The Radcliffe Infirmary is bursting the seams of its 10-acre site; the Oxford Regional Hospital Board would like to have a special hospital in the city; and the new university laboratories going up in the Keble Road Triangle will shoulder off some of the smaller medical units, such as the department of social medicine, housed in the tall Victorian houses shortly to be demolished. Luckily, by the foresight of the city council, a 60-acre site off Osler Road in Headington has been scheduled since the end of the war for further hospital development, and remains miraculously untouched by any road planner. The board of governors of the United Oxford Hospitals is certain that building here will give the necessary space for an integrated programme for undergraduate and graduate medical teaching in a centre which treats all the sick of a large community—a plan to be worked out with the regional board, the city council, and the National Health Service.

The Radcliffe Infirmary will remain the key hospital both for treatment and teaching, because it lies near the scientific departments of the university. (Already on the Radcliffe site the regius professor of medicine and the Nuffield Professors of medicine, surgery, and anæsthetics have had new additions to their departments built or firmly planned.) But the hospital consultants need new laboratory space for research, and the active Nuffield Institute for Medical Research should be far more suitably housed than in the superb Georgian "Tower of the Winds", formerly part of the Radcliffe Observatory. (This would be ideal for a graduate centre.) There is no large lecture theatre and no university department of psychiatry, and the crowded department of physical medicine is so hemmed in that the only possible expansion would be a mine shaft sunk through the hospital dispensary. The Osler Road site would get over these difficulties of growth.

A week after these plans were mooted, a memorandum entitled the "Nuffield Orthopædic Centre 1960–1970" was published by the management committee of what has been known for so long as the Wingfield-Morris Orthopædic Hospital—a hospital under the regional board, but with a professorial chair of orthopædic surgery endowed by Lord Nuffield. This describes its growth from a small convalescent home in 1871 to a modern orthopædic centre serving with its 21 peripheral clinics a population of over a million. Its future plans include an extension of the hospital itself into the unused 8 acres of its site, an enlargement of the Mary Marlborough Lodge, a new rehabilitation unit built largely by the munificence of the National Fund for Polio Research, a hostel for graduates, and a new home for night nurses which will release Pollock House as a nucleus for a new physiotherapy school, at present lacking in the region.

Certainly Lord Nuffield's innumerable gifts to promote the practice and theory of medicine in Oxford, including the £2 million pounds to develop a medical school, gave an impetus to growth which increases as the years pass, and the cooperation between the teaching group of the Oxford United Hospitals and the regional hospital board augurs well for the future.

THE M.G.H. 150

AT the end of this month the Massachusetts General Hospital is to hold a convocation in celebration of its 150th anniversary. The third general hospital to be opened in the United States, the M.G.H., besides caring for more than a million patients and training many thousands of doctors and nurses, has made very notable contributions to medicine, including the first public demonstration of ether anæsthesia in 1846. Today it has 925 beds, about a thousand students are enrolled in its educational programmes, and 160 residents and housemen continue their medical training there, as well as the students of the Harvard Medical School. Of its annual budget of 20 million dollars, more than 4 million is spent on research. Its high quality of care has attracted patients from all over the world, while student, doctors, and scientists from a great many countries have been to Boston to learn and teach at the M.G.H. and Harvard.

ISOTOPES AND TROPICAL MEDICINE

A SYMPOSIUM on the use of radioisotopes in the study of endemic and tropical diseases was held in Bangkok on Dec. 12–16 under the auspices of the International Atomic Energy Agency (I.A.E.A.) and the World Health Organisation (W.H.O.) Participants came from Australia, Ceylon, China, India, Iraq, Pakistan, the Philippines, Portugal, Sweden, Thailand, the Union of South Africa, the United Kingdom, the United States, Venezuela, and Vietnam, together with workers attached to F.A.O., I.A.E.A., and W.H.O.

The purpose was to bring together experts in tropical medicine and experts in medical uses of isotopes, and to enable them to review problems of endemic and tropical diseases which are being, or could be, investigated with isotopes. Subjects thus reviewed were protein metabolism and protein deficiencies, the anæmias and hæmoglobinopathies, tropical sprue, iron metabolism, water and electrolyte balance, endemic goitre, parasite and insect metabolism, the isotope-marking of parasites and insects, and the control of arthropod vectors of disease by irradiation and sterilisation.

Opening papers were read by P. C. C. Garnham (parasitology), L. Bruce-Chwatt (entomology), H. Foy (hæmatology), G. R. Wadsworth (nutrition), J. B. Stanbury (endemic goitre),

1. 15th report of the Nuffield Foundation, Nuffield Lodge, Regent's Park, London, N.W.1.

and C. S. Leithead (water and electrolytes). Words of caution were offered by A. S. McFarlane, who emphasised some of the difficulties of interpreting results of isotope studies, and by N. Veall, who said that isotope techniques should be used only if they were clearly superior to other methods of investigation. A fascinating item was the film shown by M. Roche (Venezuela) who, with his colleagues, has devised an elegantly simple technique for studying the sucking activity and blood uptake of the hookworm *Ancylostoma caninum*.[1]

The published proceedings should serve as a useful starting-point for those interested in this aspect of tropical medical research.

HOSPITAL COSTS IN SCOTLAND

THE analysis[2] of the running costs of Scottish hospitals for 1959–60 shows that the average weekly cost of maintaining a patient in the larger general hospitals was £22 10*s*. 11*d*., and in teaching hospitals £25 5*s*. 9*d*. The average cost of an outpatient attendance was 11*s*. 5*d*. and 12*s*. respectively. The average daily number of inpatients in hospitals of all types was 53,209, and the total number of outpatient attendances was 5,888,816. Of every £1 spent on maintaining and treating a patient in hospital, 12*s*. 1*d*. was spent on the salaries and wages of medical, nursing, and other staff, 5*s*. 1*d*. on supplies, including provision, drugs, dressings, and boiler fuel, and 2*s*. 10*d*. on such services as laundry, building maintenance, rates, postage, and telephones. The average weekly cost of provisions per person fed in hospital was £1 4*s*.

TEACHING PSYCHIATRY BY COLOUR TELEVISION

DEMONSTRATIONS of cases presented by the departments of psychological medicine and child psychiatry at Guy's Hospital were seen in London at the Royal College of Surgeons by means of colour television on a large screen on Dec. 12–14.

On the first day Dr. D. Stafford-Clark introduced a discussion on the obsessive compulsive syndrome with Mr. Murray Falconer and Sir Charles Symonds, and Sir Charles gave a clinical demonstration of neuropsychiatric assessment. On the following day Dr. Stafford-Clark showed some patients with chronic hysteria, and Dr. G. F. Vaughan introduced discussions on cerebral palsy and on preventive psychiatry in which Dr. R. C. Mac Keith, Prof. P. E. Polani, and Mrs. Jessie Williams took part. On the final day cases of dementia were demonstrated and discussed by Dr. J. J. Fleminger, Dr. I. C. K. Mackenzie, and Mr. Peter Schurr; childhood schizophrenia and a patient in psychotherapy were demonstrated by Dr. Vaughan; and the presentations were concluded with an experiment in the objective measurement of an effect of hypnosis conducted by Dr. Stephen Black.

The demonstrations were described as an experiment in communication in teaching psychiatry, and it is claimed that this is the first time that psychiatry has been presented in this way in Great Britain. The pattern used by this medical colour television unit for the past three and a half years was adopted at the meetings: the doctors in a studio may be seen on the screen in the hall, and the audience may question them through a moderator in the hall who is in touch with the studio. The remoteness of the lecturer from his audience was particularly noticeable in these meetings on psychiatry, and the only clue that reached the speaker at Guy's Hospital that he was talking over the heads of his audience were such questions from the hall as " What *is* Korsakoff's syndrome? ". We have suggested[3] that the place for the speaker is beside the screen, not on it, and that television should be used to illustrate what he has to say. The demonstration of psychiatric cases is an excellent use of television; and, as most of the patients were presented by colleagues, the presence of the speaker in the studio was unnecessary, and on occasions an embarrassment. One speaker had to look carefully round the studio before he introduced a boy, to make sure that no patient could hear what he said; an upset occurred when a child saw himself on the speaker's monitor television set; and a boy who was being demonstrated by a psychotherapist was distracted by the speaker describing what the boy should have been doing. The quality of the picture has not improved in the past few years, and it was difficult to hear some speakers clearly. There was a high background noise of machinery, telephone dialling, and a film projector from the loudspeakers; and from time to time the hospital staff-location system irritated the audience.

1. Roche, M., Torres, C. M. *Exp. Parasitol.* 1960, **9**, 250.
2. H.M. Stationery Office, 1960. 10*s*. 6*d*.
3. *Lancet*, 1960, i, 1356.

CZECHOSLOVAK MEDICAL LITERATURE

THE National Medical Library of Czechoslovakia has produced an Annual of Czechoslovak Medical Literature for 1957,[1] which lists all the books and articles on medical subjects published in Czechoslovakia in that year. In each entry the title is given in both Czech and English; and the entries are grouped under subject-headings. In addition to the various branches of medicine, the annual covers the biological sciences, and veterinary medicine.

Publishers are listed in Czech, with an English translation; a similar translation of the list of periodical titles would be welcome. An author-index prefaced, for the benefit of foreign readers, by the Czech alphabet, would greatly enhance the value of this useful annual.

THE ORAL VIBRATOR

ABOUT eighteen months ago Tait[2,3] described an oral vibrator for patients who had undergone laryngectomy. Except for the battery, the entire vibrator was contained in a dental plate. Now, thanks to the increased " miniaturisation " of electronic components, Tait has been able to design a vibrator in which both battery and oscillator are built into the plate.[4] The appliance is still under development, and Tait does not suggest that it should yet replace the normal form of oral vibrator.

The vibrator works from a 3·6 volt battery of three nickel-cadmium cells which can be recharged from time to time. The circuit, now including two transistors, has been redesigned to obviate the need for a comparatively bulky transformer. Because of the low working voltage, the loudness of the voice is less than that from the conventional vibrator. A tongue-operated switch is included; and, though this results in loss of synchronism between voice and articulation, satisfactorily intelligible speech is possible.

1. The Annual of Czechoslovak Medical Literature, 1957. Pp. 510. Obtainable from Státní Lékařská Knihovna [National Medical Library], Sokolská 31, Prague, 2, Czechoslovakia.
2. Tait, R. V. *Brit. dent. J.* 1959, **106**, 336.
3. Tait, R. V. *Lancet*, 1959, ii, 38.
4. Tait, R. V. *Brit. dent. J.* 1960, **109**, 506.

University of London

On Nov. 16 the degree of M.D. was awarded to B. M. Hibbard.

University of Durham

At a congregation on Dec. 17 the following degrees and diplomas were conferred:

M.B., B.S.—Parkash Chand Ahluwalia, R. H. Appleby, G. H. Cowling, D. D. Imrie, J. N. Mitchell, E. W. Nave, P. T. F. Newnam, Emmanuel Ezebuani Okoyeocha Horatio Okeke, * Alan Potter, * G. E. Rich, H. M. Sanderson, Elizabeth B. Taylor, Balasingam Thalayasingam, P. T. Vale, A. C. Watt.

D.P.M.—Eileen Atkinson, Brian Cornes, Kenneth Davison, Agnes W. Justice, Harry Neubauer, Joan M. Ridley, F. J. Roberts, C. K. Sutcliffe.

* in absentia.

University of Leeds

Dr. C. R. Blagg has been appointed lecturer in the department of medicine and Dr. S. J. Webb lecturer in the department of anæsthetics.

University of Wales

On Dec. 17 the following degrees were conferred:

M.D.—C. P. Seager.

M.Ch. (with distinction)—G. E. Heard.

Association of Anæsthetists of Great Britain and Ireland

The closing date for entries for the prize of 200 guineas offered by this association for an essay on general anæsthesia for dental surgery is March 1, and for prizes of £100, £50, and £25 for papers on research in anæsthesia or related subjects is March 31. Particulars may be had from the secretary of the Association, 47, Lincoln's Inn Fields, London, W.C.2.

International Congress for Microbiology

This congress will be held from Aug. 19 to 25, 1962, in Montreal.

Medical Association for the Prevention of War

On Thursday, Jan. 12, at 8 P.M., at Friends House, Euston Road, N.W.1, Prof. Alexander Haddow will speak on medicine and disarmament.

International Congress of Otorhinolaryngology

This congress will be held from July 23 to 29 in Paris. Further particulars may be had from Dr. H. Guillon, general secretary for the congress, 6, Avenue Mac-Mahon, Paris 17e, France.

Anglo-American Medical Society

A meeting of this society will be held on Saturday, Jan. 21, at 2 P.M., at the U.S.A.F. Base at Alconbury, near Huntingdon, when Dr. Julian Ward, medical adviser to the United States Pioneer Space Project, will speak on the medical aspects of space travel.

Anglo-French Exchange Bursaries

The Institut National d'Hygiène is offering short-term grants for work in France again this year to British doctors and medical research workers. Details can be had from the director, Ciba Foundation, 41, Portland Place, London, W.1. The closing date for applications is Jan. 31.

History of Medicine

The Royal Society have formed a British national committee for the history of science, under the chairmanship of Sir Harold Hartley. Medicine is to be represented by the Faculty of the History of Medicine and Pharmacy of the Society of Apothecaries.

Royal Society of Medicine

Section of Anæsthetics—This section is offering a prize (£30) for a paper by a senior registrar or registrar holding a clinical appointment in anæsthesia in the National Health Service. Fellowship of the society is not necessary for entry. Papers for the 1962 award must be submitted by Jan. 1, 1962. Further details can be had from the hon. secretary of the section, 1, Wimpole Street, London, W.1.

Central Council for Health Education

This Council's annual summer school will be held from Aug. 15 to 25 at the University College of North Wales, Neuadd Reichel, Bangor. The medical speakers will include Prof. A. L. Banks, Dr. Alfred Torrie, Dr. D. E. Parry-Pritchard, and Dr. J. J. A. Reid. Further particulars may be had from the medical director of the Council, Tavistock House North, Tavistock Square, London, W.C.1.

Reciprocity with New Zealand

The New Zealand Parliament has passed legislation making the health benefits they provide available to United Kingdom citizens visiting New Zealand. The legislation came into effect on Nov. 17. The New Zealand health service is nearly as comprehensive as the N.H.S., but it excludes spectacles, some appliances, and dental services except for young people under 19. Comprehensive reciprocal health arrangements have already been made with Denmark, Norway, Sweden, and Yugoslavia.

Scottish Hospital Endowments Research Trust

During 1958–59 the interest received from the Trust's investments amounted to £106,701, an increase of £2792 over the previous year. This increase is, in the main, due to the continuing policy of the Trustees of reinvesting parts of the endowment fund when market conditions are suitable. The market value of the fund at July 31, 1959, amounted to £2,117,150, against £2,093,598 at July 31, 1958. Research grants authorised by the Trustees during 1958–59 amounted to £92,337, and the excess of income over expenditure was £8424. Copies of the annual report and accounts may be had from H.M. Stationery Office (pp. 20. 1*s*. 3*d*.).

British Medical Association

On Thursday, Jan. 19, at 5.30 P.M., at B.M.A. House, Tavistock Square, London, W.C.1, Prof. J. H. Kellgren will open a lecture-discussion on the diagnosis and treatment of osteo-arthritis.

Horder Memorial Trust

A medical selection committee of the Royal College of Physicians of London and St. Bartholomew's Hospital has awarded the first Horder travelling fellowship to Dr. E. M. Darmady, senior pathologist to the Portsmouth and Isle of Wight area. Dr. Darmady was a former house-physician of Lord Horder. Another fellow will probably be appointed in 1964.

Food Additives

The Food Standards Committee has appointed a Food Additives and Contaminants Subcommittee to replace the Preservatives Subcommittee. The terms of reference of the new subcommittee are: " To consider problems referred to the subcommittee by the Food Standards Committee in relation to all substances added to food, whether deliberately or not ". Sir Charles Dodds is the chairman and other medical members are Dr. J. M. Johnston, Prof. Alan Kekwick, Dr. H. E. Magee, and Prof. B. S. Platt.

Army Medical Services

Major-General H. E. Knott has been appointed to be director-general of Army Medical Services, and he will succeed Lieut.-General Sir Alexander Drummond in April.

General Knott graduated M.B. from the University of Dublin in 1928 and proceeded to the degree of M.D. in 1935. He served as commandant of the Army School of Health from 1950 to 1953 and later became deputy director of Army Health, B.A.O.R. In 1955 he went to West Africa as D.D.M.S. in the rank of brigadier, and in 1957 was posted as assistant director of Medical Services, Aldershot Command. In 1958 he took up his present appointment as D.D.M.S., H.Q. Eastern Command. He was appointed honorary physician to the Queen in April, and he has been appointed C.B. in the New Year honours.

Opticians Act

An Order in Council was made on Dec. 21 bringing into operation on June 1 the remaining sections of the Opticians Act 1958.

The General Optical Council, which will keep registers of opticians who are qualified to test sight or supply glasses, was set up on Jan. 1, 1959. The sections of the Act which come into operation on June 1 will make it an offence for anyone not a registered medical practitioner or registered ophthalmic optician to test sight, and for anyone to sell glasses or any optical appliance (excluding sunglasses) except under the supervision of a registered medical practitioner or registered optician. The use of these titles by unregistered persons will become an offence. The maximum fine for conviction on any of these offences will be £250. Any opticians who have not yet registered should apply without delay to the Council.

Surgeon Captain P. de B. Turtle, R.N.R., has been appointed an honorary surgeon to the Queen in succession to Surgeon Captain J. A. Shepherd, R.N.R.

The title of the *Journal of Obstetrics and Gynæcology of the British Empire* has been changed to *Journal of Obstetrics and Gynæcology of the British Commonwealth*.

Demonstrations in psychiatry and neurology for doctors and senior medical students will be held at St. George's Hospital Medical School, London, S.W.1, at 5 P.M. on Thursdays from Jan. 12 to March 16. The speakers will be Dr. Denis Williams, Sir Paul Mallinson, Dr. Hamilton Paterson, Dr. Maurice Partridge, and Dr. Desmond Curran.

CORRIGENDUM: *Heberden Society*.—The serum-globulin level cited by Dr. J. J. Bunim (see *Lancet*, Dec. 24, p. 1380) was expressed in grammes (*not*, as we stated, milligrammes) per 100 ml.

Births, Marriages, Deaths

DEATHS

WARDILL.—On Dec. 24, at 268, Wingrove Road, Newcastle upon Tyne, William E. M. Wardill, F.R.C.S., aged 66 years, beloved husband of Wilhelmina (née Ross).